LATVIJAS UNIVERSITĀTE

Karbociklisko amīnu- potenciālo NMDA receptora antagonistu sintēze un īpašību izpēte

Promocijas darbs doktora grāda iegūšanai ķīmijas nozarē organiskās ķīmijas apakšnozarē

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Rīga, 2000

Promocijas darbs izstrādāts Latvijas Organiskās sintēzes institūtā laika posmā no 1997. gada līdz 2000. gadam.

Darba raksturs: disertācija ķīmijas nozarē organiskās ķīmijas apakšnozarē.

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Darba aizstāvēšana notiks Latvijas Universitātes ķīmijas zinātņu nozares promocijas padomes sēdē Latvijas Universitātes Ķīmijas fakultātē Kr. Valdemāra ielā 48 2000. gada 19. decembrī.

Ar disertāciju un tās kopsavilkumu var iepazīties Latvijas Universitātes bibliotēkā, Kalpaka bulvārī 4, un Latvijas Akadēmiskajā bibliotēkā, Rupniecības ielā 10.

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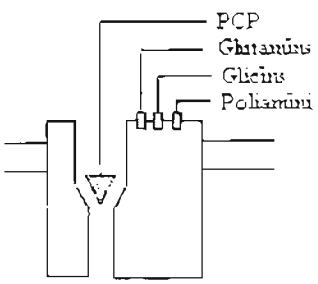
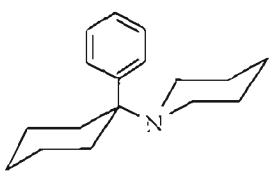
Satura rādītājs

1. Ievads

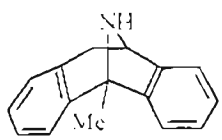
N-metil-D-aspartāta (NMDA) receptora antagonizēšana paver plašas iespējas centrālās nervu sistēmas (CNS) disfunkciju ārstēšanai, kas saistītas ar pataloģisku glutamāta producēšanos no presinaptiskajiem neironiem.[1,2] Pie šādām CNS disfunkcijām pieskaitāma gan akūta neirodeģenerācija triekas un smadzeņu traumu gadījumā, gan hroniska neirodeģenerācija Parkinsona, Alcheimera un Hantingtona slimību gadījumos.[1,3] Šī receptora antagonisti ir potenciāli preparāti arī epilepsijas, narkotisko vielu atkarības un depresijas simptomātiskajā ārstēšanā.[1,3] NMDA receptora-jonu kanāla kompleksa modulēšanu var realizēt, iedarbojoties uz tā ligandu - glutamīna, glicīna, poliamīnu un fenciklidīna (PCP) saistīšanās vietām (1. attēls).[1-3]



1. attēls



PCP



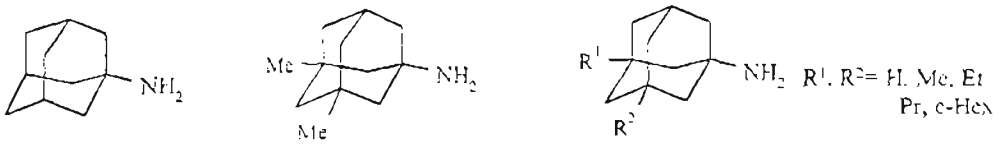
(+) MK-801

2. attēls

Jonu kanāla bloķētāji (PCP saistīšanās vietas antagonisti) nekonkurē ar endogēno signālu pārnesēju-glutamātu un saistās tikai ar ierosinātu receptoru t.i. bloķē atvērtu jonu kanālu. Šāds darbības veids nodrošina to efektivitāti arī pie pataloģiski augstas glutamāta koncentrācijas.[1-3]

Klīniskajos pētījumos augstas afinitātes NMDA nekonkurējošie antagonisti PCP un dizocilpīns ((+)MK-801) (2. attēls) terapeitiskajās devās uzrāda nevēlamus psihotropos simptomus. Tas sākotnēji noveda pie secinājuma, ka NMDA receptora nekonkurējošais antagonisms no terapeitiskā viedokļa nav izmantojams.[3] Savukārt, padziļinātos elektrofizioloģiskajos pētījumos ar plašāku savienojumu klāstu tika noskaidrots, ka nekonkurējošo antagonistu terapeitisko profilu ietekmē tādi faktori, kā receptora bloķēšanas/debloķēšanas ātrums un šī efekta atkarība no membrānas potenciāla.[1,4] Būtiski, ka šie faktori ir vairāk izteikti mērenas afinitātes nekonkurējošiem antagonistiem, kuri arī klīniskajos pētījumos uzrāda augstu terapeitisko indeksu.[4] Pašlaik vairāki šādi savienojumi tiek izmantoti klīnikā vai arī iziet klīniskās pārbaudes dažādām CNS

disfunkciju indikācijām (piem. ADCI, budipīns, felbamāts, remacemīds, cerestats u.c.).[1] Bez jau pieminētajiem savienojumiem nekonkurējošie mērenas afinitātes NMDA receptora antagonisti ir arī firmas *Merz&Co* preparāti adamantān-1-amīns (amantadīns) un 3,5-dimetiladamantān-1-amīns (memantīns) (3.attēls).[1,3,5-7]



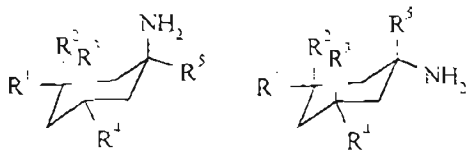
Amantadīns **Memantīns** **3,5-aizvietotie adamantān-1-amīni**

3. attēls

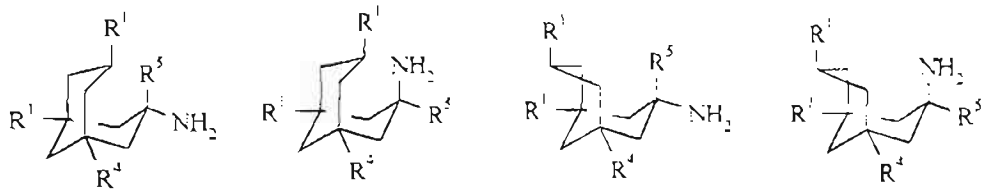
Šie preparāti jau vairākus gadus tiek izmantoti klīnikā Parkinsona slimības, kā arī smadzeņu dementes ārstēšanai, un terapeitiskajās devās reti uzrāda nevēlamus blakus efektus. Memantīna terapija CNS slimību ārstēšanā ir bijusi īpaši veiksmīga (15 gadu laikā ārstēto dementes pacientu skaits pārsniedz 200 000).[3]

Lai radītu jaunus CNS aktīvus preparātus, mērķtiecīga ir memantīnam strukturāli radniecīgu savienojumu izpēte. Līdz šim sintezēti un *in vivo* pārbaudīti galvenokārt amantadīna un memantīna homologi 3,5-aizvietotie adamantān-1-amīni (3. attēls) un to N-alkilatvasinājumi.[5-7] Tomēr, tikai daži šīs klases savienojumi (R^1=Me, R^2=Et; R^1= R^2=Et) uzrāda vērā ņemamu NMDA receptora afinitāti, tāpēc ir ļoti maz informācijas par šāda tipa savienojumu struktūras - receptora afinitātes un citu biofizikālo parametru likumsakarībām.

Mūsu darba pamatuzdevums bija izstrādāt sintēzes metodes karbociklisķajiem amīniem, kas ir strukturāli radniecīgi 3,5-aizvietotajiem adamantān-1-amīniem. Par šādiem struktūranalogiem var uzskatīt 1,3,5-aizvietotos cikloheksānamīnus (4. attēls) un 1,3,5,7-aizvietotos biciklo[3.3.1]nonān-3-amīnus (4. attēls), kuros no adamantān-1-amīna struktūras saglabāti attiecīgi viens un divi cikloheksāna fragmenti. Aizvietotāji šajās molekulās dotu iespēju variēt molekulas telpiskos izmērus, kas sniegtu informāciju par karbociklisko amīnu lipofīlās daļas ietekmi uz receptora saistību. Jāatzīmē, ka nesimetriski 1,3,5-aizvietotajiem cikloheksānamīniem ir iespējami divi diastereomēri, savukārt 1,3,5,7-aizvietotajiem biciklo[3.3.1]nonān-3-amīniem iespējami četri izomēri. Svarīgi ir iegūt atsevišķi diastereomērus ar fiksētu aminogrupas novietojumu, kas ļautu novērtēt aminogrupas telpiskās orientācijas ietekmi uz receptora saistību.



1,3,5-Aizvietotie cikloheksânamîni



1,3,5,7-Aizvietotie biciklo[3.3.1]nonân-3-amîni

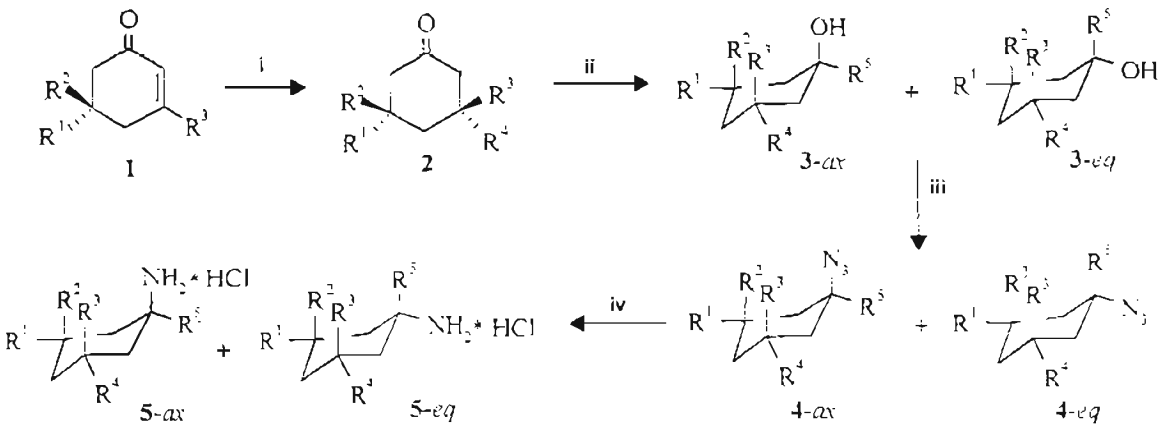
4. attēls

Galvenā sintētiskā problēma mērķa savienojumu iegūšanai ir saistīta ar aminogrupas ievadīšanu pie trešējā oglekļa atoma. Preparatīvi nozīmīgākā literatūrā piedāvātā pieeja *terc*-karbīnamīnu sintēzei[8] ir *in situ* ģenerētu karbkatjonu reakcija ar slāpekļūdeņražskābi (HN_3) vai nitriliem (Ritera reakcija). Lai gan azidēšanas reakcija ir efektīva sintētiskā metode, tās galvenais trūkums ir eksplozīvās HN_3 izmantošana. Savukārt, Ritera reakcija ciklisko *terc*-karbīnamīnu iegūšanai pamatā aprobežojas ar toksiskās zilskābes izmantošanu kā nitrila komponenti. Mērķa savienojumu sintēzes kontekstā paredzējām veikt pētījumu par Ritera reakcijas izmantošanas iespējām *terc*-karbīnamīnu liela apjoma sintēzēm, izvairoties no toksiskiem un dārgiem reaģentiem.

Nesimetriski 1,3,5-aizvietoto cikloheksānamīnu un biciklo[3.3.1]nonān-3-amīnu iegūšanā ļoti nozīmīga ir aminofunkcijas ievadīšanas diastereoselektivitāte. No teorētiskā viedokļa īpaši interesanta ir Ritera reakcijas stereoķīmija, kas līdz šim maz pētīta. Ņemot vērā šīs reakcijas praktisko nozīmi, kā vienu no promocijas darba uzdevumiem izvirzījām Ritera reakcijas diastereoselektivitātes likumsakarību noskaidrošanu.

2. 1,3,5-Alkilaizvietoto cikloheksānamīnu sintēze

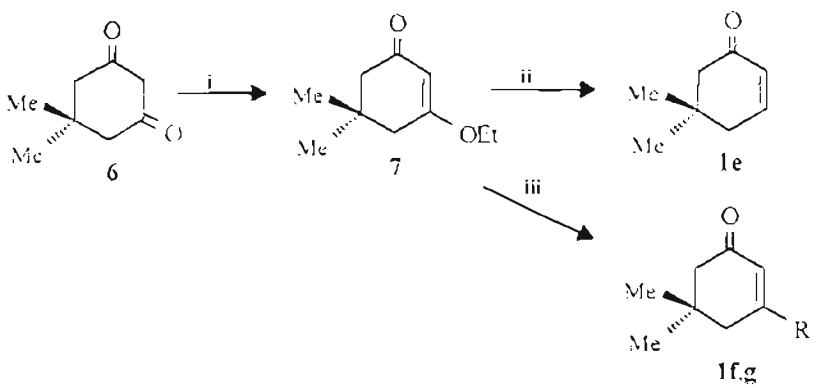
1,3,5-Alkilaizvietoto cikloheksānamīnu **5a-p** sintēzi (1. shēma) veicām, sākot no 2-cikloheksēn-1-oniem **1a-g**, kuri apkopoti 1. tabulā.



Reakcijas apstākļi. i: R^4_2CuMgX, Et_2O; ii: R^5MgX, Et_2O; iii: A metode: HN_3, $TiCl_4$, $CHCl_3$; B metode: $TMSN_3$, $BF_3{*}Et_2O$, benzols; iv: $LiAlH_4$, Et_2O pēc tam HCl.

1. shēma

Izejas savienojumi **1a-d** ir komerciāli pieejami. Pārejos cikloheksēnonus **1e-g** ieguvām pēc literatūrā[9] aprakstītās metodes (2. shēma).



Reakcijas apstākļi. i: EtOH, TsOH ii: $LiAlH_4$, pēc tam 10% H_2SO_4; iii: RMgI pēc tam 5% H_2SO_4

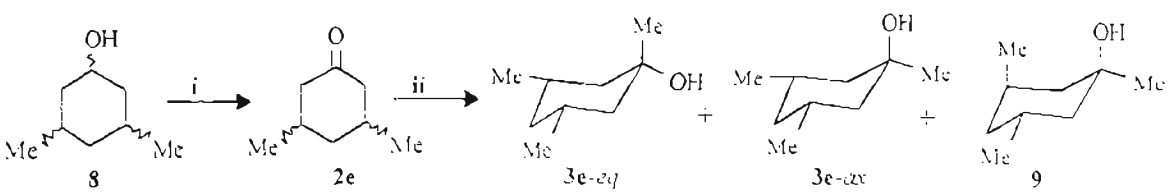
2. shēma

2-Cikloheksēn-1-onus **1a-g** 1,4-konjugētās pievienošanas reakcijā ar organokuprātiem (iegūti *in situ* no alkilmagnija halogenīdiem un vara (I) hlorīda) pārvērtām par cikloheksanoniem **2a-d** un **2f-m** (1. shēma, 2. tabula). Cikloheksēnona **1c** gadījumā dietil- un dipropilmagnija kuprāti pievienojās ar augstu diastereoselektivitāti, selektīvi veidojot izomērus **2g** un **2h**, kuros 3- un 5-metilgrupas novietotas *cis* konfigurācijā (> 95%, GC). Šāds rezultāts ir saskaņā ar vara organisko savienojumu anti-paralēlo

pievienošanās virzienu 5-aizvietotajiem cikloheksēnoniem.[10] Apstiprinājumu 3. un 5. pozīcijas metilgrupu *cis*- konfigurācijai ieguvām, analizējot mērķa savienojumu **5g** un **5h** PMR spektru datus (sk. 2.2. nodaļu).

Ketonus **2a-d** un **2f-m** Grinjāra reakcijā ar alkilmagnija halogenīdiem pārvērtām par cikloheksanoliem **2a-d** un **2f-m** (1. shēma, 3. tabula). Šajā reakcijā 3-monoaizvietotie cikloheksanoni **2a-c** deva izomēro cikloheksanolu **3a-c**-*ax** un **3a-c**-*eq** maisījumu, savukārt 3,3,5-trīsaizvietotie cikloheksanoni **2f-j** veidoja cikloheksanolus **3f-j**-*ax* kā vienīgos reakcijas produktus. Šāds stereoķīmiskais iznākums ir sakaņā ar literatūras datiem par nukleofīlās pievienošanās virzienu 3-metil- un 3,3,5-trimetilcikloheksanoniem.[11]

1,*c*-3,*c*-5-Trimetilcikloheksān-*r*-1-olu **3e**-*eq* ieguvām, izmantojot citu sintēzes ceļu (3. shēma). Oksidējot komerciāli pieejamo 3,5-dimetilcikloheksanola **8** izomēru maisījumu, ieguvām *cis*- un *trans*-dimetilcikloheksanonus **2e**. Dimetilcikloheksanona **2e** izomēru sadalīšana ir literatūrā aprakstīta[12] tomēr ievērojami ērtāk izrādījās atdalīt cikloheksanolu **3e**-*eq* ar nepieciešamo 3,5-metilgrupu *cis*-konfigurāciju no izomēro cikloheksanolu **3e**-*eq*, **3e**-*ax* un **9** maisījuma, kuru ieguvām ketona **2e** reakcijā ar metilmagnija jodīdu.



Reakcijas apstākļi: i: H_2SO_4, CrO_3; ii: MeMgX

3. shēma

Trešējo spirtu **3a-m** transformācija par amīniem **5a-p** ir mērķa savienojumu sintēzes noteicošais posms. Efektīvākās metodes trešējo spirtu pārvēršanai par *terc*-karbīnamīniem ir *in situ* ģenerēto karbkatjonu reakcija ar slāpekļūdeņražskābi[13] vai tās ekvivalentu azidotrimetilsilānu ($TMSN_3$)[14] un nitriliem (Ritera reakcija). Kā parādīts 5. nodaļā uz 1,3-dimetil un 1,3,3,5-tetrametilcikloheksanolu **3a** un **3f** piemēra. Ritera reakcija ļauj iegūt tikai vienu amīna izomēru, attiecīgi **5a**-*ax* un **5f**-*ax*, jo atbilstošie formamīdi Ritera reakcijā veidojas ar augstu diastereoselektivitāti. Savukārt,

* Apzīmējumi –*ax* un –*eq* norāda heteroatoma aksiālo vai ekvatoriālo novietojumu diastereomērā cikloheksāna atvasinājuma pamatkonformācijā (5. un 6. attēlu)

cikloheksanolu **3a** un **3f** azidēšanas reakcijā ar apmierinošu iznākumu veidojās abi azīdu **4a** un **4f** izomēri (4. tabula), kurus viegli varēja sadalīt, izmantojot kolonu hromatogrāfiju. Tāpēc, ņemot vērā, ka darba mērķis bija iegūt abus cikloheksānamīnu **5a-c** un **5e-j** diastereomērus, 1,3,5-aizvietoto cikloheksānamīnu **5** sintēzei izvēlējāmies cikloheksanolu **3** azidēšanas reakciju.

Spirtus **3a-p** pārvērtām par azīdiem **4a-p** (1. shēma, 4. tabula), kā reaģentus izmantojot gan HN_3 un titāna tetrahlorīdu[13] (A metode, 4. tabula), gan $TMSN_3$ un bora trifluorīda ēterātu[14] (B metode, 4. tabula). Jāatzīmē, ka B metode ir ievērojami ērtāka, jo tajā eksplozīvā un toksiskā skābe HN_3 tiek aizstāta ar komerciāli pieejamo un mazāk bīstamo $TMSN_3$. Diastereomēro spirtu **3a-c** gadījumā azidēšanas reakciju izdarījām ar izomēru maisījumu, jo abi spirta izomēri dod vienādu izomēro azīdu attiecību.[13]

Azidēšanas reakcijā iegūtos diastereomēros azidocikloheksāna atvasinājumus **4a-c**-*ax*,-*eq* un **4e-j**-*ax*,-*eq* veiksmīgi sadalījām, izmantojot kolonu hromatogrāfiju. Azidocikloheksānus **4a-p** ar litija alumohidrīdu[15] reducējām par amīniem **5a-p**, kurus izdalījām hidrogenhlorīdu veidā (1. shēma, 5. tabula). Diastereomēro azidocikloheksānu **4a-c**,**4e-j**-*ax* un **4a-c**,**4e-j**-*eq* gadījumā ieguvām tīrus cikloheksānamīnu diasteromērus **5a-c**,**e-j** -*ax* un **5a-c**,**e-j**-*eq*.

1. tabula Aizvietotie 2-cikloheksēn-1-oni **1a-g**

Savienojums	R^1	R^2	R^3	Iznākums,[a] %
1a	H	H	H	
1b	H	H	Me	
1c	H	Me	Me	
1d	Me	Me	Me	
1e	Me	Me	H	70
1f	Me	Me	Et	40
1g	Me	Me	Pr	40

[a]ja iznākums nav uzrādīts, savienojums ir komerciāli pieejams;

2. tabula Aizvietotie cikloheksanoni **2a-m**

Savienojums	R^1	R^2	R^3	R^4	Iznākums,[a] %
2a	H	H	H	Me	
2b	H	H	H	Et	63
2c	H	H	H	Pr	79
2d	H	H	Me	Me	78
2e	Me	H	H(Me)	Me(H)	86[b]
2f	Me	H	Me	Me	57
2g	Me	H	Et	Me	78
2h	Me	H	Pr	Me	82
2i	Me	Me	H	Et	54
2j	Me	Me	H	Pr	74
2k	Me	Me	Me	Me	
2l	Me	Me	Et	Et	84
2m	Me	Me	Pr	Pr	79

[a]ja iznākums nav uzrādīts, savienojums ir komerciāli pieejams;
[b]iegūts oksidējot 3,5-dimetilcikloheksanolu (5. shēma)

3. tabula Aizvietotie cikloheksanoli **3a-p**

Savienojums	R^1	R^2	R^3	R^4	R^5	Iznākums,[a] %
3a-*ax*, **3a**-*eq*,	H	H	H	Me	Me	88
3b-*ax*, **3b**-*eq*,	H	H	H	Et	Me	93
3c-*ax*, **3c**-*eq*	H	H	H	Pr	Me	93
3d	H	H	Me	Me	Me	78
3e-*eq*	Me	H	H	Me	Me	15
3f-*ax*	Me	H	Me	Me	Me	85
3g-*ax*	Me	H	Et	Me	Me	94
3h-*ax*	Me	H	Pr	Me	Me	88
3i-*ax*	Me	Me	H	Et	Me	84
3j-*ax*	Me	Me	H	Pr	Me	88
3k	Me	Me	Me	Me	Me	93
3l	Me	Me	Me	Me	Et	92
3m	Me	Me	Me	Me	Pr	85
3n	Me	Me	Et	Et	Me	87
3o	Me	Me	Pr	Pr	Me	90
3p	H	H	H	H	Me	

[a]ja iznākums nav uzrādīts, savienojums ir komerciāli pieejams

4. tabula Aizvietotie azidocikloheksāni **4a-p**

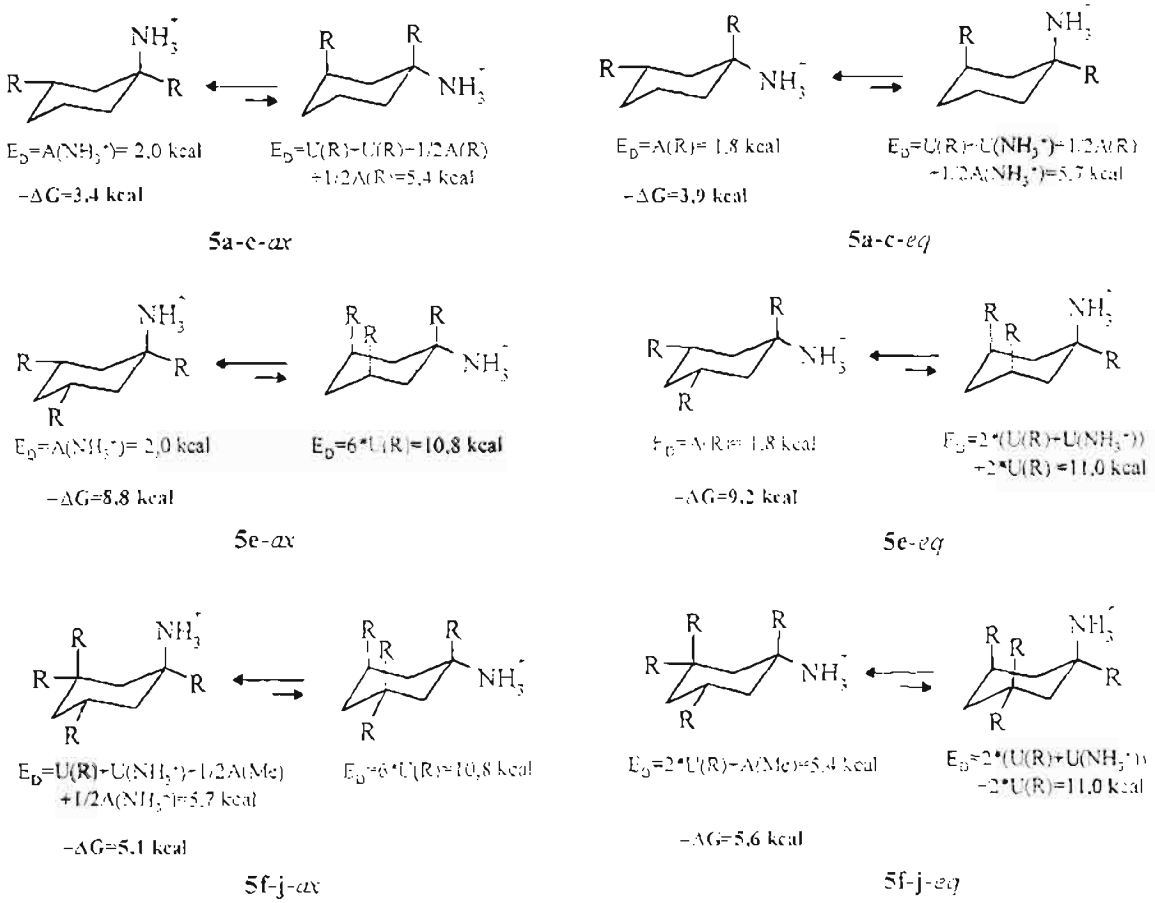
Savienojums	R^1	R^2	R^3	R^4	R^5	Metode	Iznākums, %
4a-*ax*	H	H	H	Me	Me	B	24
4a-*eq*							12
4b-*ax*	H	H	H	Et	Me	A	26
4b-*eq*							4
4c-*ax*	H	H	H	Pr	Me	A	24
4c-*eq*							11
4d	H	H	Me	Me	Me	A	65
4e-*ax*	Me	H	H	Me	Me	B	43
4e-*eq*							19
4f-*ax*	Me	H	Me	Me	Me	A	42
4f-*eq*							12
4g-*ax*	Me	H	Et	Me	Me	A	47
4g-*eq*							12
4h-*ax*	Me	H	Pr	Me	Me	A	44
4h-*eq*							9
4i-*ax*	Me	Me	H	Et	Me	B	45
4i-*eq*							12
4j-*ax*	Me	Me	H	Pr	Me	A	54
4j-*eq*							7
4k	Me	Me	Me	Me	Me	A	67
4l	Me	Me	Me	Me	Et	A	39
4m	Me	Me	Me	Me	Pr	A	65
4n	Me	Me	Et	Et	Me	A	66
4o	Me	Me	Pr	Pr	Me	A	61
4p	H	H	H	H	Me	A	27

5. tabula Aizvietoto cikloheksānamīnu hidrogenhlorīdi **5a-p**

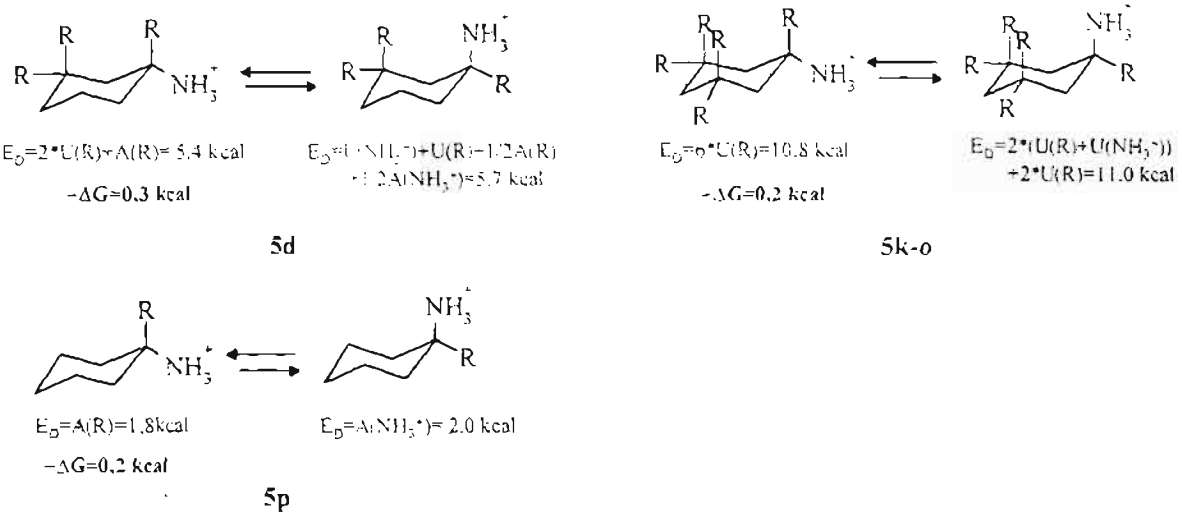
Savienojums	R^1	R^2	R^3	R^4	R^5	Iznākums, %
5a-*ax*	H	H	H	Me	Me	63
5a-*eq*						48
5b-*ax*	H	H	H	Et	Me	66
5b-*eq*						43
5c-*ax*	H	H	H	Pr	Me	80
5c-*eq*						81
5d	H	H	Me	Me	Me	73
5e-*ax*	Me	H	H	Me	Me	74
5e-*eq*						55
5f-*ax*	Me	H	Me	Me	Me	74
5f-*eq*						57
5g-*ax*	Me	H	Et	Me	Me	68
5g-*eq*						60
5h-*ax*	Me	H	Pr	Me	Me	57
5h-*eq*						36
5i-*ax*	Me	Me	H	Et	Me	69
5i-*eq*						44
5j-*ax*	Me	Me	H	Pr	Me	83
5j-*eq*						44
5k	Me	Me	Me	Me	Me	82
5l	Me	Me	Me	Me	Et	74
5m	Me	Me	Me	Me	Pr	88
5n	Me	Me	Et	Et	Me	78
5o	Me	Me	Pr	Pr	Me	72
5p	H	H	H	H	Me	69

2.1. 1,3,5-Aizvietoto cikloheksānamīnu konformāciju analīze

Sintezēto cikloheksānamīnu hidrogenhlorīdu **5a-p** konformāciju analīzi (5. un 6. attēls) veicām semikvantitatīvi, konformāciju destabilizācijas enerģiju (E_D) aprēķināšanai izmantojot aizvietotāju A un U vērtības (A(R)=U(R)=1,8 kcal (R=Me, Et, Pr): $A(NH_3^+)=U(NH_3^+)=2,0$ kcal).[16] Pēc semikvatitatīvajiem aprēķiniem amīnu izomēriem **5a-c**-*ax*, **5e**-*ax* un **5f-j**-*ax* konformācija ar aksiāli novietotu aminogrupu ir enerģētiski izdevīgāka par 3,4 kcal/mol, 8.8 kcal/mol un 5,1 kcal/mol, attiecīgi. Diastereomēriem **5a-c**-*eq*, **5e**-*eq* un **5f-j**-*eq* konformācija ar ekvatoriāli novietotu aminogrupu ir enerģētiski izdevīgāka par 3,9 kcal/mol, 9,2 kcal/mol un 5.6 kcal/mol, attiecīgi. Šāda enerģiju starpība pēc Bolcmaņa sadalījuma[17] atbilst >99% stabilākā konformēra populācijai, tāpēc cikloheksānamīnu **5a-c** un **5e-j** diastereomērus var uzskatīt par konformacionāli ierobežotiem ar fiksētu protonētas aminogrupas aksiālo vai attiecīgi ekvatoriālo novietojumu.



5. attēls



6. attēls

Simetriski aizvietoto cikloheksānamīnu **5d** un **5k-p** gadījumā konformērs ar ekvatoriāli novietoto aminogrupu ir enerģētiski izdevīgāks tikai par 0.2-0.3 kcal/mol. Tas norāda, ka abas šo savienojumu konformācijas ir apdzīvotas līdzīgi.

2.2. 1,3,5-Aizvietoto cikloheksānamīnu aizvietotāju konfigurācijas pierādīšana

Aminogrupas konfigurāciju 1,3-diaizvietoto cikloheksānamīnu diastereomēros **5a-c** un 1,3,5-trimetilcikloheksilamīnā **5e** nevar viennozīmīgi noteikt, izmantojot tikai ^{1}H-KMR spektru datus, jo šo savienojumu viegli interpretējamo metilgrupu protonu ķīmisko nobīžu atšķirība ir neliela (6. tabula). Šim nolūkam informatīvi bija amīnu **5a**-*ax* un **5a**-*eq* ^{13}C-KMR spektri. Amīnu diastereomēru **5a**-*ax* un **5a**-*eq* ^{13}C-KMR spektru signālus korelējām ar literatūrā[18] interpretēto 1,3-dimetilcikloheksanolu **3a**-*ax* un **3a**-*eq* spektru datiem. Līdzīgi kā cikloheksanolu gadījumā γ-efekta ietekmē amīna **5a**-*ax* 1-metilgrupas signāls ir nobīdīts vājākā laukā par 5.8 m.d., salīdzinot ar tā izomēru **5a**-*eq*.

Būtiski, ka amīnam **5a**-*ax* gāzu hromatogrāfiskajā analīzē iznākšanas laiks ir par 0.2 min īsāks kā izomēram **5a**-*eq*. Šāda īpašība ir novērota arī konformacionāli ierobežotiem cikloheksanoliem.[19] Tā tiek skaidrota ar viršanas temperatūru starpību, ko rada aksiālā aizvietotāja mazāka spēja veidot ūdeņraža saiti, salīdzinot ar ekvatoriālo aizvietotāju. Pamatojoties uz iznākšanas laiku starpību gāzu hromatogrāfiskajā analīzē, varējām izdarīt secinājumus par cikloheksānamīna **5a** homologu **5b**, **5c** un **5e** diastereomēru aminogrupas konfigurāciju.

1,3,3,5-Tetraaizvietoto cikloheksānamīnu **5e-j** aizvietotāju konfigurācijas noteikšanai izmantojām ^{1}H-KMR spektru datus (6. tabula). Aksiāli novietotās 3-metilgrupas protonu signāli savienojumiem **5e,f,i,j**-*ax* ir nobīdīti vājākā laukā par ~0,25 m.d., salīdzinot ar attiecīgajiem izomēriem **5e,f,i,j**-*eq*. Ievērojamā ķīmisko nobīžu starpība ir izskaidrojama ar 1,3-diaksiālo aizvietotāju σ kompresijas efektu. Šis efekts stiprāk izteikts elektronegatīvajai aksiālajai 1-aminogrupai savienojumos **5e,f,i,j**-*ax*, salīdzinot ar aksiālo 1-metilgrupu savienojumos **5e,f,i,j**-*eq* (literatūrā[20,21] aprakstīta šāda efekta ietekme uz 1,3,5-aizvietoto cikloheksanolu metilgrupu protonu ķīmiskajām nobīdēm). 3-Etil- un 3-propil-1,3,5-trimetilcikloheksānamīnu izomēriem **5g**-*ax* un **5h**-*ax* aksiālās aminogrupas σ kompresijas efekts uz 3. pozīcijas metilgrupu PMR spektros nav novērojams. Tas apstiprina 3. un 5. pozīcijas metilgrupu *cis* konfigurāciju savienojumos **5g** un **5h** (abas metilgrupas novietotas ekvatoriāli).

Nelielu 3. pozīcijas aksiālo aizvietotāju σ kompresijas efektu (0,03-0,16 ppm) uz 1-metilgrupas protonu ķīmiskajām nobīdēm var novērot arī 1,3,3,5-tetraaizvietoto cikloheksānamīnu **5f-j**-*eq* spektros salīdzinājumā ar to izomēriem **5f-j**-*ax*.

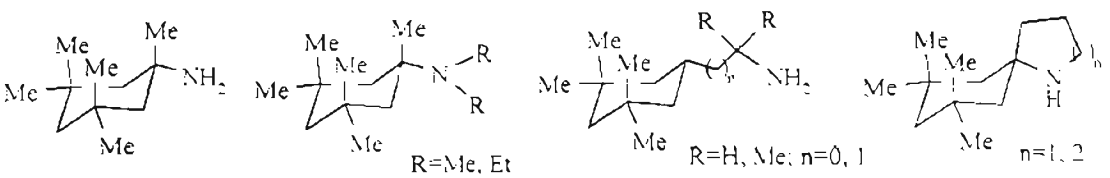
Papildus aminogrupas konfigurācijas pierādījums 1,3,3,5-tetraaizvietotajos cikloheksānamīnos **5e-j** ir izomēru **5e-j**-*ax* īsāks iznākšanas laiks (~0,5 min) gāzu hromatogrāfiskajā analīzē, salīdzinot ar izomēriem **5e-j**-*eq*.

6. tabula Diastereomēro cikloheksānamīnu **5-*ax*** un **5-*eq*** metilgrupu protonu ķīmiskās nobīdes

Amīns	1-CH_3	3-CH_3(ax)	3-CH_3(eq)	5-CH_3(eq)
5a-*ax*	1.45	-	0.89	-
5a-*eq*	1.47	-	0.91	-
5b-*ax*	1.46	-	-	-
5b-*eq*	1.45	-	-	-
5c-*ax*	1.45	-	-	-
5c-*eq*	1.47	-	-	-
5e-*ax*	1.44	-	0.90	0.90
5e-*eq*	1.47	-	0.90	0.90
5f-*ax*	1.45	1.23	0.91	0.90
5f-*eq*	1.61	1.04	1.00	0.96
5g-*ax*	1.48	-	0.84	0.85-0.95
5g-*eq*	1.55	-	0.88	0.91
5h-*ax*	1.51	-	0.86	0.89
5h-*eq*	1.54	-	0.8-0.95	0.8-0.95
5i-*ax*	1.46	1.23	0.92	-
5i-*eq*	1.56	0.98	0.96	-
5j-*ax*	1.45	1.23	0.92	-
5j-*eq*	1.55	0.98	0.95	-

3. 1,3,3,5,5-Pentametilcikloheksānamīna struktūranalogu sintēze

No 2. nodaļā sintezētajiem 1,3,5-aizvietotajiem cikloheksānamīniem **5a-p** 1,3,3,5,5-pentametilcikloheksānamīns (**5k**) uzrādīja visaugstāko afinitāti uz NMDA receptoru *in vitro* (sk. 7. nodaļu, 13. tabulu), kā arī daudzsološu terapeitisko profilu *in vivo*.[22] Tāpēc tālākai struktūras optimizēšanai bija mērķtiecīgi sintezēt šī savienojuma struktūranalogus - N-alkil atvasinājumus **10a-c**, aminoalkilcikloheksānus **11a-c** un 1-azaspiro-dekānu un undekānu **12a,b**.

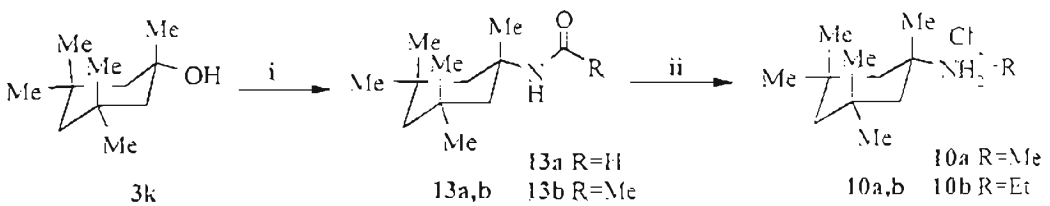


5k **10a-c** **11a-c** **12a,b**

7. attēls

3.1. 1,3,3,5,5-Pentametilcikloheksānamīna N-alkil atvasinājumu sintēze

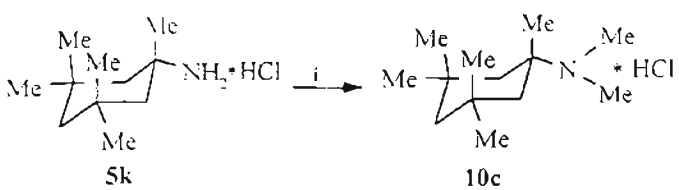
1,3,3,5,5-Pentametilcikloheksānamīna N-alkil atvasinājumu **10a-c** sintēzei izmantojām tradicionālās C-N saites veidošanas metodes. N-Metil- un N-etil- 1,3,3,5,5-pentametilcikloheksānamīnus **10a,b** ieguvām, reducējot attiecīgos N-formil un N-acetil atvasinājumus **13a,b** (4. shēma).[23] Amīdu **13a,b** iegūšana no cikloheksanola **3k** plašāk apskatīta 6. nodaļā.



3k **13a,b** **10a,b**

Reakcijas apstākļi un iznākumi. i: a) TMSCN, H_2SO_4, AcOH, 78%; b) MeCN, H_2SO_4, 60%; ii: $LiAlH_4$, Et_2O, pēc tam HCl a) 86% b) 82%.

4. shēma



5k **10c**

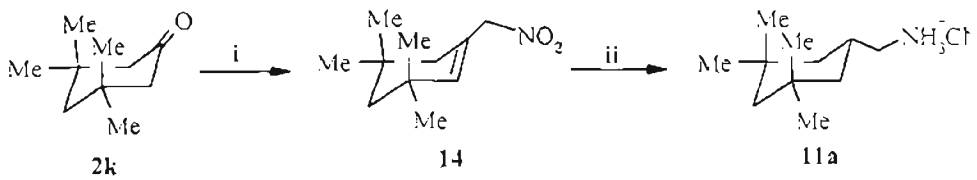
Reakcijas apstākļi un iznākumi. i: NaOH, H_2O, Et_2O, pēc tam HCO_2H, H_2CO, pēc tam HCl, 83%

5. shēma

N,N-Dimetil-1,3,3,5,5-pentametilcikloheksānamīnu **10c** ieguvām amīna **5k** reducējošā alkilēšanā pēc Ešveilera-Klarka metodes[24] (5. shēma).

3.2. 1-(Aminoalkil)-3,3,5,5-tetrametilcikloheksānu sintēze

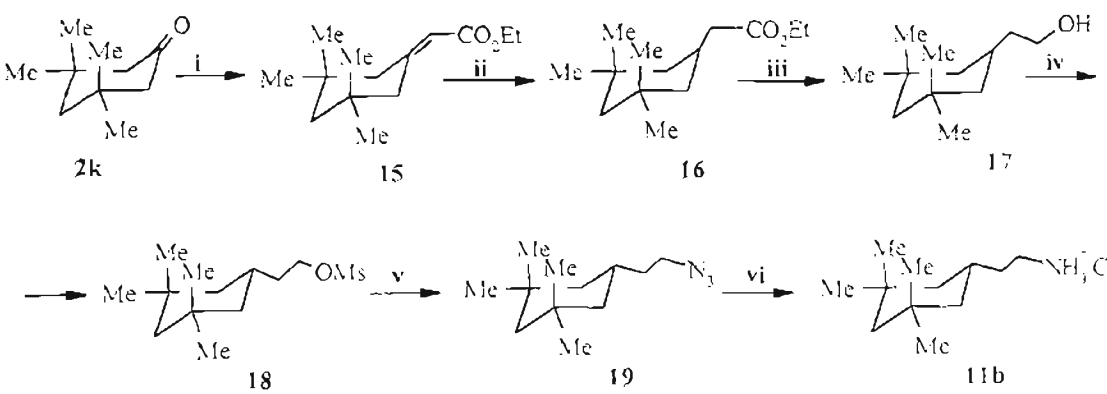
1-(Aminometil)-3,3,5,5-tetrametilcikloheksānamīna **11a** (6. shēma) sintēzi veicām, izmantojot ketona **2k** Henri-tipa kondensāciju ar nitrometānu, pēc literatūrā aprakstītās procedūras ketosteroīdu modificēšanai.[25] Hidrogenējot nepiesātināto nitrosavienojumu **14** hidrogenhlorīda donora- hloroforma klātbūtnē, ieguvām mērķa savienojumu **11a**.[26]



Reakcijas apstākļi un iznākumi. i: a) $MeNO_2$, etilēndiamīns, 61%; ii: H_2, 10% Pd/C, CH_3Cl, MeOH, 50%.

6. shēma

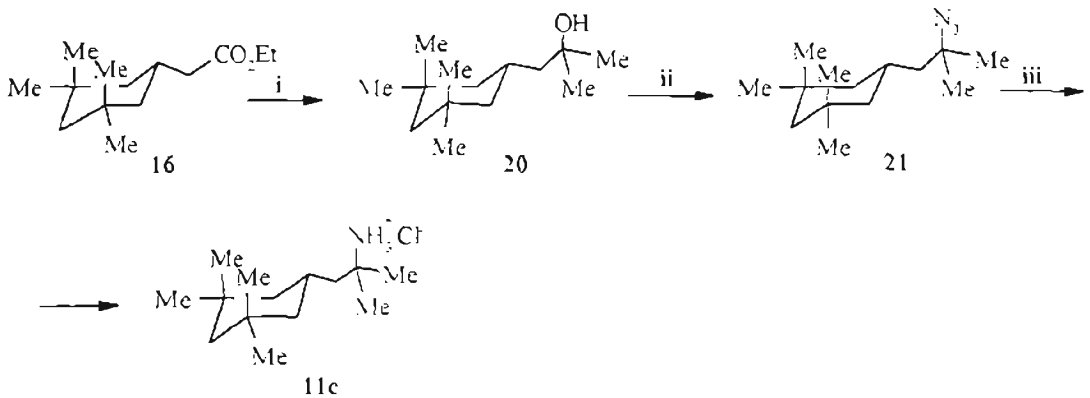
Lai iegūtu aminoetilcikloheksāna atvasinājumu **11b** (7. shēma), C-C saites veidošanai izmantojām ketona **2k** Hornera-Vardšofa-Emonsa reakciju ar trietilfosfonātu.[27] Tālāk, nepiesātināto esteri **15** hidrogenējām un ieguvām esteri **16**. To, savukārt, reducējām ar litija alumīnija hidrīdu par hidroksietilcikloheksāna atvasinājumu **17**, kuru mezilējām un mezilgrupu savienojumā **18** nomainījām pret azido grupu.[28] Iegūto azīdu **19** reducējot,[15] ieguvām mērķa savienojumu- 1-(2-aminoetil)-3,3,5,5-tetrametilcikloheksānu (**11b**).



Reakcijas apstākļi un iznākumi. i: $(EtO)_2POCH_2CO_2Et$, NaH, THF, 86%; ii: H_2, 10% Pd/C, EtOH, 95% iii: $LiAlH_4$, Et_2O, 79%; iv: MsCl, Et_3N, benzols, 94%; v: NaN_3, DMSO, 80%; vi: $LiAlH_4$, Et_2O, pēc tam HCl 83%.

7. shēma

Esteri **16** izmantojām kā izejvielu 1-(2-amino-2-metilpropil)-3,3,5,5-tetrametilcikloheksāna **11c** iegūšanai (8. shēma). No estera **16** Grinjāra reakcijā ieguvām trešējo spirtu **20**, kuru, savukārt, azidēšanas reakcijā[14] pārvērtām par azīdu **21**. Reducējot azīdu **21**, ieguvām mērķa savienojumu **11c**.

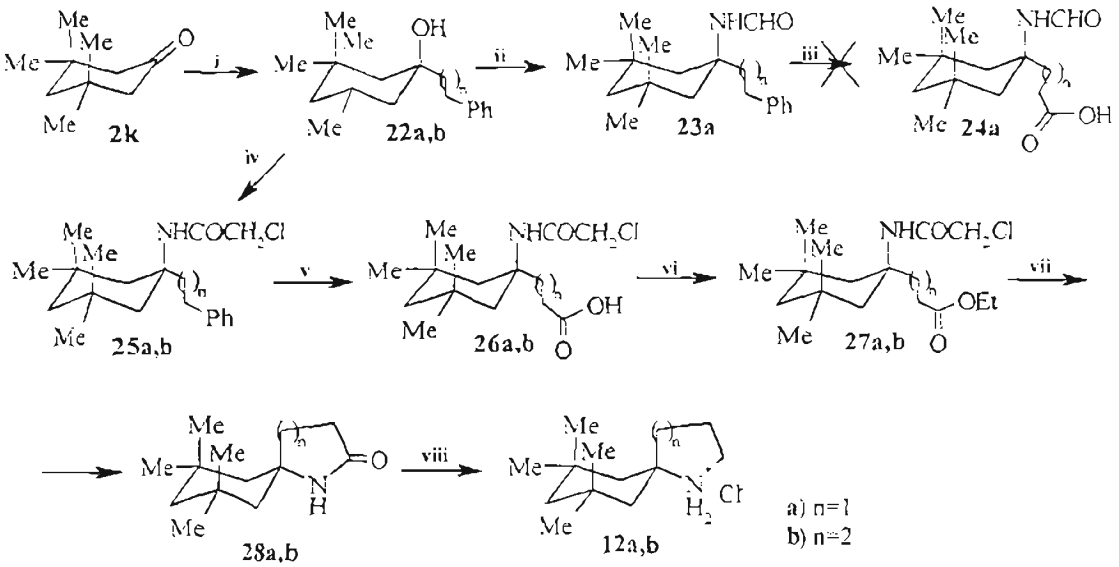


Reakcijas apstākļi un iznākumi. i: MeMgI, Et_2O 80%; ii: $TMSN_3$, BF_3*Et_2O, benzols 52%; iii: $LiAlH_4$, Et_2O, pēc tam HCl 89%.

8. shēma

3.3. 7,7,9,9-Tetrametil-1-azaspiro[4.5]dekāna un 8,8,10,10-tetrametil-1-azaspiro [5.5]undekāna sintēze

Viena no visbiežāk izmantotajām pieejām 1-azaspiro[4.5]dekāna atvasinājumu iegūšanai balstās uz nitrocikloheksānu Mihaela reakciju ar nepiesātinātajiem esteriem, ar sekojošu nitrogrupas reducēšanu un spirocikliska laktāma veidošanos.[29,30,31] Šī pieeja ir izmantota arī 1-azaspiro[5.5]undekāna atvasinājumu iegūšanai, ķīmiskajās pārvērtībās pagarinot oksikarboniletil fragmentu par vienu C atomu.[32] Lai pielietotu Mihaela pievienošanas reakciju 1-azaspiroalkānu sintēzē, kā izejviela bija nepieciešams 1-nitro-3,3,5,5-tetrametilcikloheksāns, kuru ar zināmajām nitrocikloheksānu sintēzes metodēm[30,33] iegūt neizdevās. Grūtības, kas saistītas ar nitrocikloalkānu iegūšanu, kā arī šaurais metožu klāsts dažāda ciklu lieluma 1-azaspiro[x,y]alkānu iegūšanai pamudināja mūs izstrādāt principiāli jaunu, vispārīgu pieeju 1-azaspirocikloalkānu sintēzei. Tā balstās uz azacikla konstruēšanu, laktamizējot aminoskābes atvasinājumu, kuru iegūst no atbilstošā 1-(fenilalkil)-cikloheksanola. Trešējais spirts kalpo kā Ritera reakcijas substrāts aminogrupas ievadīšanai. Savukārt, fenilgrupa tiek izmantota kā latentā karboksilgrupa. Šīs metodes iespējas demonstrējām uz mērķa savienojumu **12a,b** sintēzes piemēra (9. shēma).



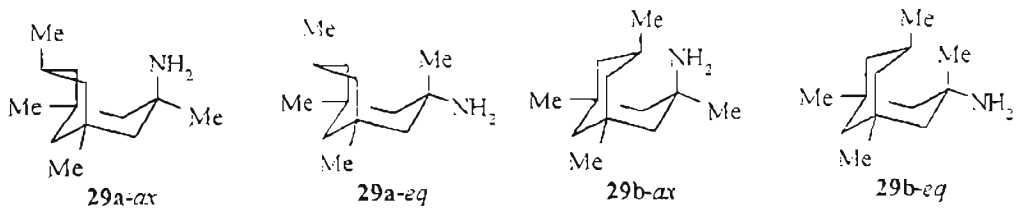
Reakcijas apstākļi un iznākumi. i: a) $Ph(CH_2)_2MgBr$, Et_2O, 88% b) $Ph(CH_2)_3MgBr$, Et_2O, 90%; ii: TMSCN, H_2SO_4, AcOH, 85%; iii: RuO_2, $NaIO_4$, MeCN, H_2O, $CHCl_3$, 0%; iv: $ClCH_2CN$, H_2SO_4, AcOH a) 96% b) 37%; v: RuO_2, $NaIO_4$, MeCN, H_2O, $CHCl_3$, a) 53% b) 74 %; vi: EtOH, $SOCl_2$, a) 78% b) 98 %; vii: tiourīnviela, AcOH, EtOH, a) 35% b) 76 %; viii: BH_3, THF, pēc tam HCl a) 44%, b) 45%.

9. shēma

Ketona **2k** reakcijā ar 2-fenetilmagnija bromīdu un 3-fenilpropilmagnija bromīdu ieguvām trešējos spirtus **22a** un **22b**, attiecīgi. Spirta **22a** gadījumā aminogrupas ievešanai sākotnēji izmantojām Ritera reakciju ar TMSCN (sk. 6. nodaļu). Taču, mēģinot oksidēt fenilgrupu formamīdā **23a**, ieguvām neidentificētu produktu maisījumu. Iespējamais šāda neveiksmīga rezultāta izskaidrojums ir nevēlama formilgrupas oksidēšanās. Fenilgrupas oksidēšanai piemērota izrādījās hloracetamidogrupa amīdos **25a,b**, kurus ieguvām cikloheksanolu **22a,b** Ritera reakcijā ar hloracetonitrilu (sk. 6. nodaļu). Oksidēšanas reakcijā iegūtās N-aizsargātās aminoskābes **26a,b** esterificējām. No esteriem **27a,b**, ar tiourīnvielu nošķeļot aizsarggrupu (sk. 6. nodaļu), veidojās laktāmi **28a,b**. Laktāmus reducējām ar borānu[34] un ieguvām attiecīgo 7,7,9,9-tetrametil-1-azaspiro[4.5]dekānu (**12a**) un 8,8,10,10-tetrametil-1-azaspiro[5.5]undekānu (**12b**).

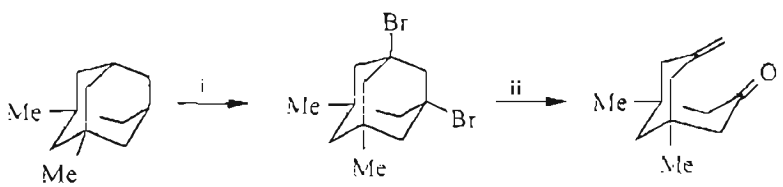
4. 1,3,5,7-Tetrametilbiciklo[3.3.1]nonān-3-amīnu sintēze

Kā jau ievadā minēts, viens no darba mērķiem bija memantīna struktūranalogu-1,3,5,7-aizvietoto biciklo[3.3.1]nonānamīnu iegūšana. Sintēzes izstrādāšanai, kā relatīvi vienkāršākos par mērķa savienojumiem izvēlējāmies 1,3,5,7-tetrametilbiciklo[3.3.1] nonānamīnus **29a**-*ax*,*eq* un **29b**-*ax*,*eq*.



8. attēls

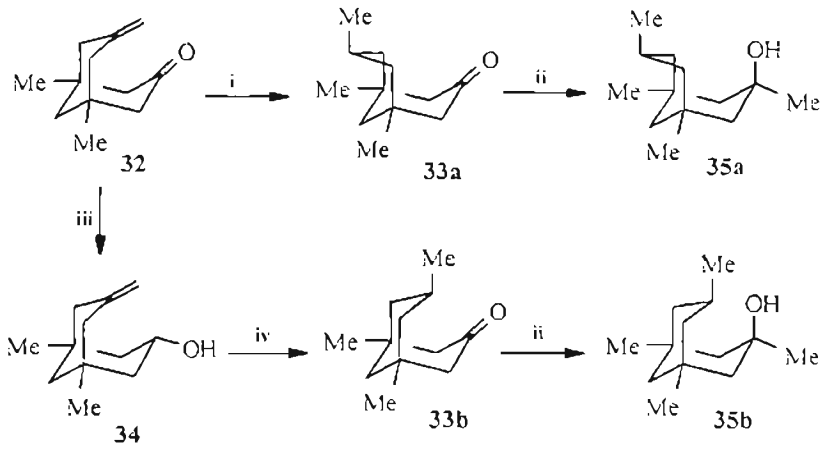
Amīnu **29a,b** sintēzes pirmais posms ir izomēro ketonu - 1,3,5,7α- un 7β-tetrametilbiciklo[3.3.1]nonān-3-onu **33a** un **33b** iegūšana. Ketonus **33a,b** ieguvām analoģiski aprakstītajai to vienkāršāko homologu 7α- un 7β-metilbiciklo[3.3.1]nonān-3-onu sintēzei (11. shēma). Bromējot komerciāli pieejamo 1,3-dimetiladamantānu **30**,[35] ieguvām 1,3-dibrom-5,7-dimetiladamantānu **31**, kuru Grobsa fragmentācijas reakcijā transformējām par 7-metilēn-1,5-dimetilbiciklononān-3-onu **32**[36] (10. shēma).



Reakcijas apstākļi un iznākumi. i: Br_2, Fe, 83%; ii: NaOH, dioksāns, 79%.

10. shēma

Hidrogenējot nepiesātināto ketonu **32**,[37] ieguvām 1,5,7α-trimetilbiciklononān-3-onu **33a** (11. shēma). Izmantojot izomēro 1,5,7β-trimetilbiciklononān-3-onu **33b** kā standartu, pārliecinājāmies, ka hidrogenēšanas reakcija ir ļoti selektīva t.i. gāzu hromatogrāfiskajā analīzē tika konstatēts, ka otra izomēra reakcijas maisījumā ir mazāk par 2%. 1,5,7β-Trimetilbiciklononān-3-onu **33b** ieguvām divās stadijās, kas ietver nepiesātinātā ketona **32** Merveina-Pondorfa-Verleja reducēšanu[38] un skābes katalizētu protona pārnesi[39] 7-metilēn-1,5-dimetilbiciklononān-3β-olā **34** (11. shēma).



Reakcijas apstākļi un iznākumi. i: H_2, PtO_2, AcOH 34 %; ii: "MeCeCl$_2$", THF, 97%; iii: Al(i-PrOH)$_3$, toluols, 57%; iv: 75% H_2SO_4, 73%.

11. shēma

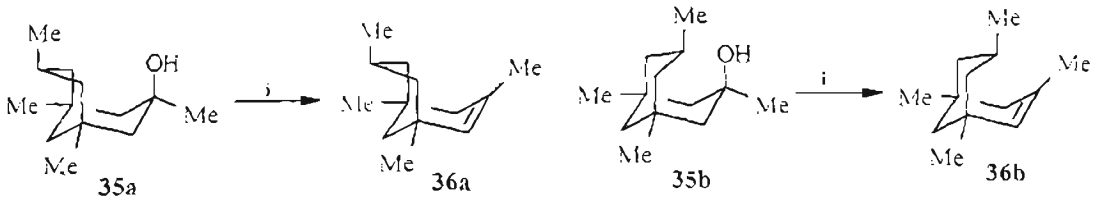
Nākošais sintēzes posms bija metilgrupas ievadīšana biciklononāna 3. pozīcijā. No literatūras zināms, ka biciklo[3.3.1]nonān-3-ons neveido pievienošanas produktus ar alkilmagnija un alkillitija reaģentiem,[40] savukārt, organolantanoīdu reaģenti pievienojas karbonilgrupai ievērojami efektīvāk.[41] 1,5,7-Trimetilbiciklonananoni **33a** un **33b** reakcijā ar metilmagnija jodīdu un metillitiju deva zemu vai vidēju konversiju par atbilstošajiem spirtiem **35a** un **35b**. Savukārt, reaģents, kas pagatavots no metilmagnija jodīda un cērija trihlorīda, kvantitatīvi pievienojās ketonu **33a** un **33b** karbonilgrupai, veidojot spirtus **35a** un **35b** ar ļoti labiem iznākumiem (7. tabula).

7. tabula Izomēro biciklononananonu **33** konversija par trešējiem spirtiem **35** reakcijā ar organometāliskajiem reaģentiem

Npk.	Reakcijas apstākļi	Konversija par trešējiem spirtiem 35, %[a]	
		35a	35b
1	MeMgI/ Et_2O	50	9
2	MeLi/ THF	70	40
3	MeMgI. $CeCl_3$/THF	100	100

a) Konversija noteikta pēc ketonu **33** un spirtu **35** attiecības gāzuhromatogrāfiskajā analīzē

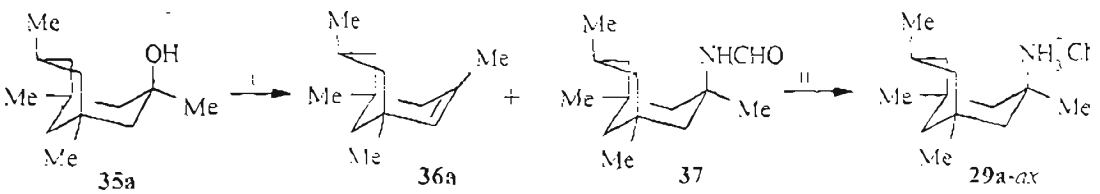
Mēģinājums realizēt spirtu **35a** un **35b** azidēšanas reakciju[14] bija nesekmīgs. Šajā reakcijā kā galvenos produktus ieguvām biciklononēnus **36a** un **36b** (12. shēma).



Reakcijas apstākļi un iznākumi. i: $TMSN_3$, $BF_3{*}EtO_2$, benzols, **36a** 45 % un **36b** 54%.

12. shēma

1,3β,5,7α-Tetrametilbiciklo[3.3.1]nonān-3α-ols (**35a**) Ritera reakcijā ar trimetilsililcianīdu[42] (sk. 5. nodaļu) deva 1,3β,5,7α-tetrametilbiciklo[3.3.1]non-2-ēnu (**36a**) un *N*-formil-1,3,5,7-tetrametilbiciklo[3.3.1]nonān-3-amīnu **37** (13. shēma).

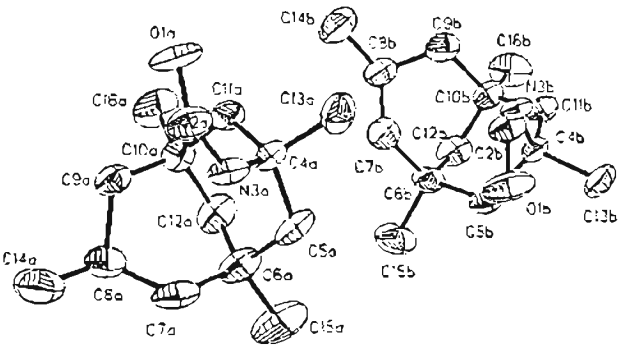


Reakcijas apstākļi un iznākumi. i: TMSCN, H_2SO_4, AcOH, **36a** 34%, **37** 55% ii: H_2O, 71%.

13. shēma

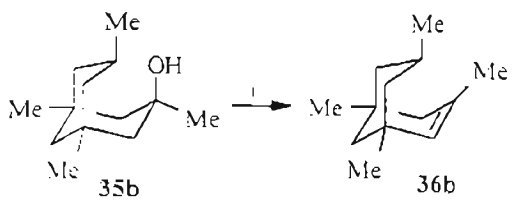
Gāzhromatogrāfiskā analīze parādīja, ka šajā reakcijā veidojas tikai viens amīda izomērs. Pārējo signālu intensitāte (ar līdzīgu iznākšanas laiku) bija nenozīmīga (<1%). Reakcijas produkta **37** PMR spektrs N-formilgrupas *cis-trans* izomērijas dēļ ir grūti interpretējams. Formamīda **37** hidrolīzes produkta **29a**-*ax* (13. shēma) gāzu hromatogrāfiskā analīze un ^{1}H-NMR kā arī ^{13}C-NMR spektri pārliecinoši parādīja, ka radies tikai viens no diviem iespējamiem amīna izomēriem. Formamidogrupas vai aminogrupas konfigurāciju biciklononāna atvasinājumos **37** un **29a**-*ax*, izmantojot ^{1}H-NMR spektru datus nevarēja noteikt, jo šajos savienojumos nerealizējas protonu vicinālās spinu-spinu mijiedarbības. Formamīda **37** rentgenstruktūras analīze parādīja, ka savienojums **37** ieņem krēsla-vannas konformāciju ar formamidogrupu *endo*-konfigurācijā (9. attēls).

Selektīva formamīda **37** veidošanās parāda, ka Ritera reakcijā amīds rodas ievērojami ātrāk, nitrilam pievienojoties no stēriski vairāk traucētās karbkatjona *endo*-puses. Šis interesantais rezultāts izskaidrots 5. nodaļā par Ritera reakcijas diastereoselektivitātes likumsakarībām.



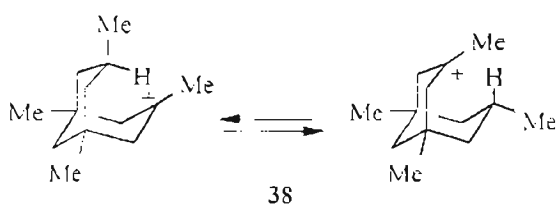
9. attēls

7β-Metilbiciklononanols **35b** atšķirībā no tā epimēra **35a** Ritera reakcijā deva 1,3,5,7β-tetrametilbiciklo[3.3.1]non-2-ēnu (**36b**) kā galveno reakcijas produktu (93% no reakcijas produktiem pēc gāzu hromatogrāfijas datiem) (14. shēma).



14. shēma

Ir zināms, ka 7β-metilbiciklononān-3-il katjonā **38** realizējas ātra transanulārā hidrīda pārnese un tas ieņem krēsla-krēsla konformāciju[37] (10. attēls). Rezultātā katjona *endo*-puse ir stēriski nosegta. Tas varētu izskaidrot, kāpēc biciklononanols **35b** Ritera reakcijā vēlamo produktu neveido.

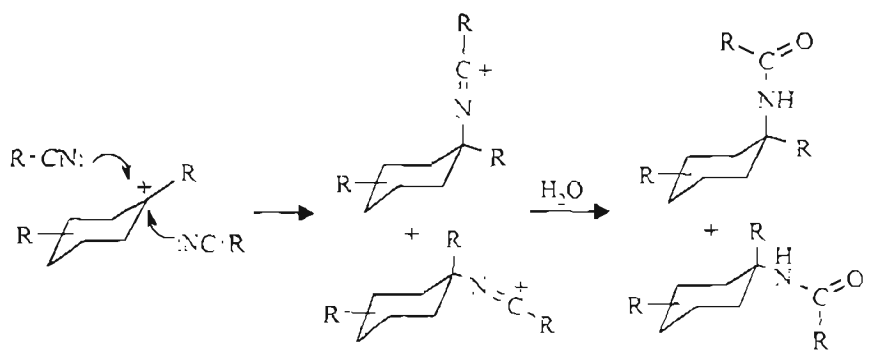


10. attēls

Ņemot vērā, ka no četriem iecerētajiem mērķa savienojumiem **29a**-*ax*, **29a**-*eq* un **29b**-*ax*, **29b**-*eq* izdevās iegūt tikai 1,3β,5,7α-tetrametilbiciklo[3.3.1]nonān-3α-amīna hidrogenhlorīdu **29a**-*ax*, kurš bioloģiskajos pētījumos uzrādīja ievērojami zemāku NMDA receptora afinitāti kā memantīns, šīs klases savienojumu sintēzi neturpinājām.

5. Ritera reakcijas diastereoselektivitāte

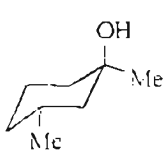
Nesimetriski 1,3,5-aizvietoto cikloheksānamīnu (sk. 2. nodaļu) un 1,3,5,7-tetrametilbiciklo[3.3.1]nonān-3-amīnu (sk. 4. nodaļu) iegūšanai ļoti nozīmīga ir informācija par aminofunkcijas ievadīšanas stereoķīmiju. *In situ* ģenerētu karbkatjonu reakcija ar nitriliem (Ritera reakcija[43]) ir viena no sintētiski nozīmīgākajām metodēm aminofunkcijas ievadīšanai pie trešējā oglekļa atoma. Neskatoties uz Ritera reakcijas praktisko nozīmi *terc*-karbīnamīnu iegūšanā,[43,44] literatūrā ir ļoti maz datu par šīs reakcijas diastereoselektivitātes likumsakarībām. Līdz šim pētīta tikai 4-aizvietoto cikloheksilkatjonu reakcija ar nitriliem un parādīts, ka nitrili ar augstu diastereoselektivitāti pievienojas no karbkatjonu aksiālās puses (11. attēls).[45,46,47] Šāds stereoķīmiskais iznākums tiek skaidrots ar cikloheksāna 2,6-aksiālo ūdeņraža atomu radīto torsijas spriegumu pārejas stāvoklī, analoģiski Felkina-Āna teorijai par nukleofīlu pievienošanos cikloheksanoniem.[46,47]



11. attēls

Lai iegūtu plašāku informāciju par Ritera reakcijas stereoķīmiju, mēs pētījām nitrilu pievienošanās diastereoselektivitāti karbkatjoniem ar dažādu stērisko apkārtni. Karbkatjonu ģenerēšanai izmantojām sekojošus trešējos cikloalkanolus:

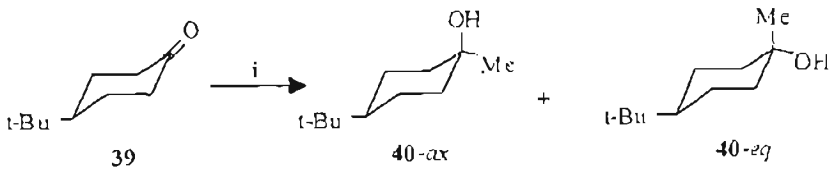
a) 1,*t*-3-dimetilcikloheksān-*r*-1-ola (**3a**-*ax*) (12. attēls) iegūšana aprakstīta 2. nodaļā. Ritera reakcijas pētījumiem izmantojām tikai izomēru **3a**-*ax*, kuru hromatogrāfiski atdalījām no diastereomēro spirtu maisījuma;



3a-*ax*

12. attēls

b) *c*-4-*terc*-butil-1-metilcikloheksān-*r*-1-olu (**40**-*ax*) un *t*-4-*terc*-butil-1-metilcikloheksān -*r*-1-olu (**40**-*eq*) ieguvām 4-*terc*-butilcikloheksanona (**39**) reakcijā ar metillitiju[46] (15. shēma) un hromatogrāfiski sadalījām izomēru maisījumu:

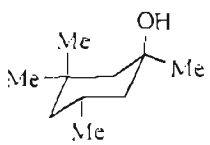


39 **40**-*ax* **40**-*eq*

Reakcijas apstākļi un iznākumi i: MeLi, Et_2O, **40**-*ax* 65%, **40**-*eq* 26%.

15. shēma

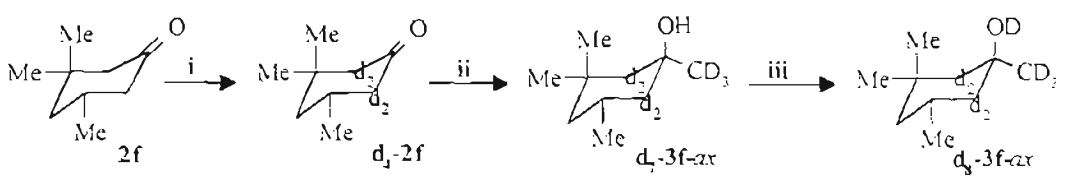
c) 1,3,3,*t*-5-tetrametilcikloheksān-*r*-1-ola (**3f**) (13. attēls) iegūšana aprakstīta 2. nodaļā:



3f-*ax*

13. attēls

d) 1,3,3,*t*-5-tetrametilcikloheksān-*r*-1-ola (**3f**) deiteroanaloga $\mathbf{d_8}$-**3f** iegūšanai kā izejvielu izmantojām cikloheksanonu **2f**, kura α-protonus bāziskā vidē aizvietojām ar deitēriju.[48] Deiterēto ketonu $\mathbf{d_4}$-**2f** Grinjāra reakcijā ar deiterēto metilmagnija jodīdu pārvērtām par cikloheksanolu $\mathbf{d_7}$-**3f**, kura hidroksilgrupas protonu arī apmainījām ar deitēriju un ieguvām cikloheksanolu $\mathbf{d_8}$-**3f**.



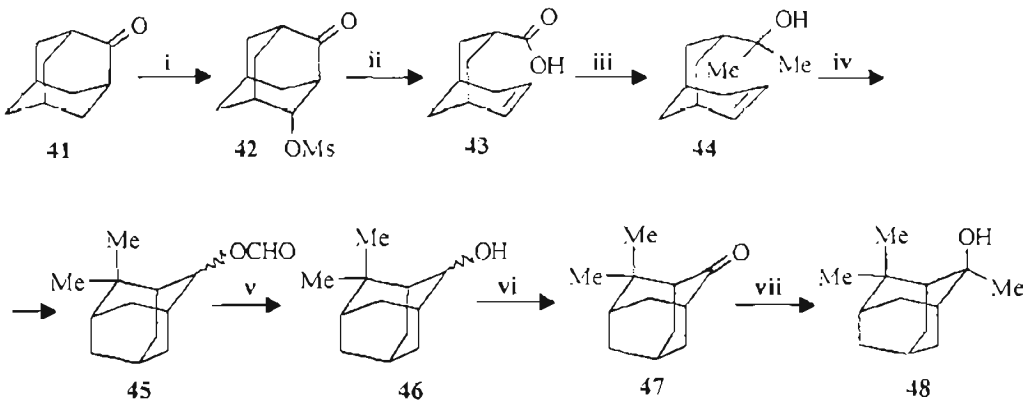
2f $\mathbf{d_4}$-**2f** $\mathbf{d_7}$-**3f**-*ax* $\mathbf{d_8}$-**3f**-*ax*

Reakcijas apstākļi un iznākumi i: D_2O, K_2CO_3, 82%, ii: CD_3MgBr, Et_2O, 83%, iii: D_2O, Et_2O, 91%

16. shēma

e) 2,4,4-trimetiladamantān-2-ola (**48**) sintēzi (17. shēma) realizējām saskaņā ar literatūras procedūru.[49] Komerciāli pieejamo adamantān-2-onu (**41**) bez starpprodukta **42** izdalīšanas transformējām par biciklo[3.3.1]non-6-ēn-3-karbonskābi (**43**), no kuras reakcijā ar metillitiju ieguvām trešējo spirtu **44**. To, savukārt, bez starpproduktu izdalīšanas pārvērtām par 4,4-dimetiladamantān-2-onu (**47**) ķīmiskajās transformācijās, kas ietver: spirta **44** ciklizāciju skābā vidē, veidojot adamantilformiātu **45**; formilgrupas noškelšanu savienojumā **45** un adamantanola **46**

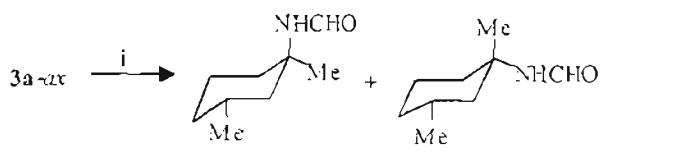
oksidēšanu par ketonu **47**. Ketons **47** reakcijā ar metillitiju stereoselektīvi veidoja mums nepieciešamo adamantanola atvasinājumu **48**.



Reakcijas apstākļi un iznākumi. **i**: NaN_3, $MeSO_3H$. **ii**: 2*N* KOH, 69% no **41**, **iii**: MeLi, Et_2O, 88%, **iv**: HCO_2H, **v**: $LiAlH_4$, Et_2O, **vi**: PDC, CH_2Cl_2, **vii**: MeLi, Et_2O. 56% no **43**.

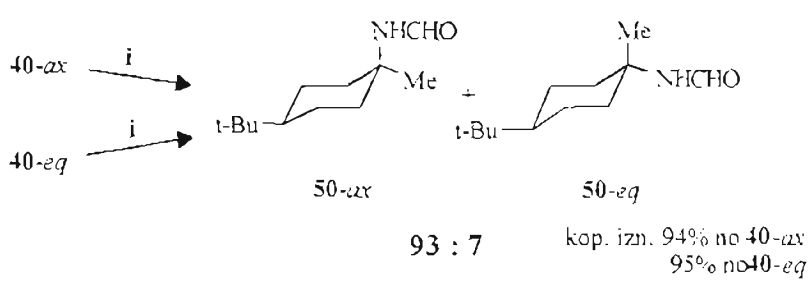
17. shēma

Ritera reakciju ar cikloalkanoliem **3a**-*ax*, **40**-*ax*, **40**-*eq*, **3f**-*ax*, d_8-**3f**-*ax* un **48** realizējām tradicionālajos apstākļos.[42] kā nitrila komponenti izmantojot HCN, ko ģenerē *in situ* no TMSCN (sk. 6. nodaļu) (18-22. shēmas).



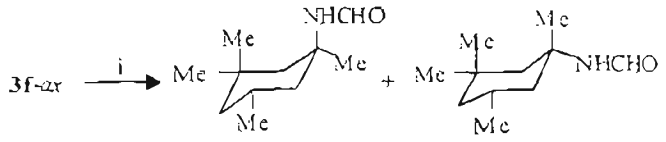
Reakcijas apstākļi. **i**: TMSCN, H_2SO_4, AcOH, 23 h, i.t

18. shēma



Reakcijas apstākļi. **i**: TMSCN, H_2SO_4, AcOH, 23 h, i.t

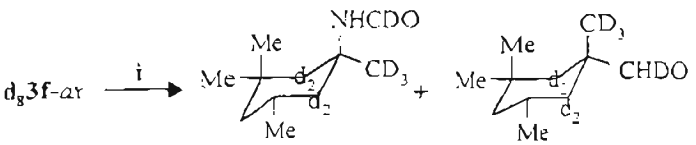
19. shēma



51-*ax* **94 : 6** **51**-*eq* kop. izn. 96%

Reakcijas apstākļi. i: TMSCN, H_2SO_4, AcOH, 23 h, i.t.

20. shēma

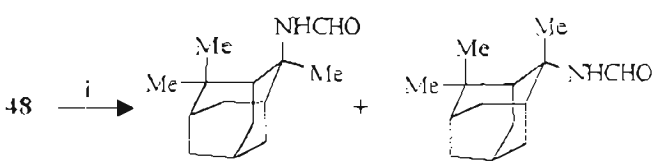


d_8-**51**-*ax* d_8-**51**-*eq* kop. izn. 71%

88 : 12

Reakcijas apstākļi. i: TMSCN, D_2SO_4, AcOD, 23 h, i.t

21. shēma



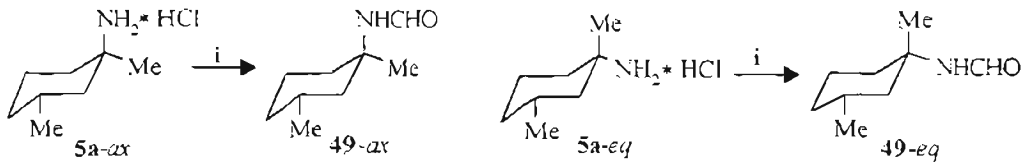
52-*ax* **52**-*eq* kop. izn. 76%

79 : 21

Reakcijas apstākļi. i: TMSCN, H_2SO_4, AcOH, 23 h, i.t

22. shēma

Reakcijā iegūto diastereomēro amīdu **49-52**-*ax-eq* un d_8-**51**-*ax-eq* attiecību noteicām ar gāzu hromatogrāfijas metodi. Amīdu **49**-*ax* un **49**-*eq* diastereomēru sadalīšana nebija iespējama, tāpēc hromatogrāfiskajai analīzei un amīdu maisījuma PMR spektru analīzei nepieciešamos standartus ieguvām, formilējot diastereomēros amīnus **5a**-*ax* un **5a**-*eq* (23. shēma) (amīnu sintēze aprakstīta 2. nodaļā). Amīdu **50-52**-*ax-eq* gadījumā diastereomērus sadalījām ar kolonu hromatogrāfijas palīdzību un pēc struktūras noskaidrošanas izmantojām kā standartus Ritera reakcijas produktu hromatogrāfiskajai analīzei.

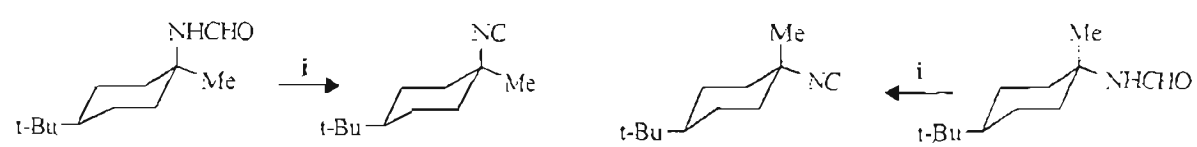


Reakcijas apstākļi. i: a) 10% NaOH; b) Ac_2O, HCO_2H, 65% **49**-*ax* un 58% **49**-*eq*.

23. shēma

Kā liecina Ritera reakcijas pētījumā iegūtie rezultāti, neskatoties uz to, ka *in situ* ģenerētais karbkatjons ir stēriski nosegts no aksiālās puses ar 3-pozīcijas metilgrupu, visos gadījumos ar lielu pārsvaru rodas aksiālā amīda izomērs. Tas ir pretrunā ar paredzamo stereoķīmisko iznākumu, ja par modeli izvēlas cikloheksanonu reakciju ar nukleofīliem, kuros 3-pozīcijas aksiālais aizvietotājs ar augstu selektivitāti virza nukleofīla uzbrukumu karbonilgrupai no ekvatoriālās puses.[11] Tāpēc dominējošu aksiālo amīdu **49-52**-*ax* un **d$_8$-51**-*ax* veidošanos Ritera reakcijā nevar izskaidrot ar kinētiski kontrolētu nitrila pievienošanos karbkatjonam.

Lai izskaidrotu iegūtos rezultātus, izvirzījām hipotēzi, ka Ritera reakcijas diastereoselektivitāti nosaka termodinamiski kontrolēta produktu veidošanās. Saskaņā ar ieteikto Ritera reakcijas mehānismu,[43] tās pirmais posms ir nitrīlija jona veidošanās, tālāk notiek ūdens molekulas pievienošanās un rodas amīds (11. attēls). Uz amīda **50**-*eq* piemēra pārliecinājāmies, ka mūsu izmantotajos Ritera reakcijas apstākļos izomērais amīds **50**-*ax* neveidojas, tātad atbilstošā nitrīlija jona pārvēršana par amīdu ir neapgriezenisks process. Lai pētītu nitrīlija jonu epimerizāciju, bija nepieciešams *in situ* ģenerēt diastereomēros nitrīlija jonus. Alternatīvi nitrilu reakcijai ar karbkatjoniem, nitrīlija jonus var ģenerēt, protonējot izonitrilus.[43] Pētījumiem nepieciešamos izonitrilu izomērus **53**-*ax* un **53**-*eq* ieguvām, dehidratējot amīdus **50**-*ax* un **50**-*eq* (24. shēma).[50]



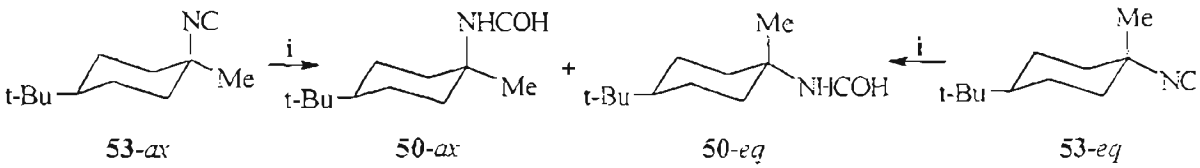
50-*ax* **53**-*ax* **53**-*eq* **50**-*eq*

Reakcijas apstākļi. i: i-Pr_2EtN, Tf_2O, CH_2Cl_2, -70°C, **53**-*ax* 48%, **53**-*eq* 76%.

24. shēma

Ritera reakcijas apstākļos no diastereomērajiem izonitriliem **53**-*ax* un **53**-*eq* ģenerējām nitrīlija jonus un reakcijas gaitu kontrolējām ar gāzu hromatogrāfijas palīdzību (25. shēma). Iegūtie rezultāti parādīja, ka *in situ* ģenerētie nitrīlija joni **54**-*ax* un **54**-*eq* savā

starpā epimerizējas (26. shēma), kā rezultātā veidojas abu izomēro amīdu maisījums ar aksiālā amīda **50**-*ax* pārsvaru (8. tabula). Tā kā nitrīlija jonu epimerizācija notiek ātrāk nekā ūdens molekulas pievienošanās, var uzskatīt, ka diastereomēro amīdu veidošanās Ritera reakcijā ir termodinamiski kontrolēta. Tomēr no izonitrila **53**-*eq* un tā izomēra **53**-*ax* iegūto amīdu **50**-*ax* un **50**-*eq* attiecība atšķiras. Tas norāda, ka, iespējams, termodinamiskā kontrole šajā reakcijā nav pilnīga.



53-*ax* **50**-*ax* **50**-*eq* **53**-*eq*

Reakcijas apstākļi: i: TMSCN, H_2SO_4, AcOH, 23h, i.t.

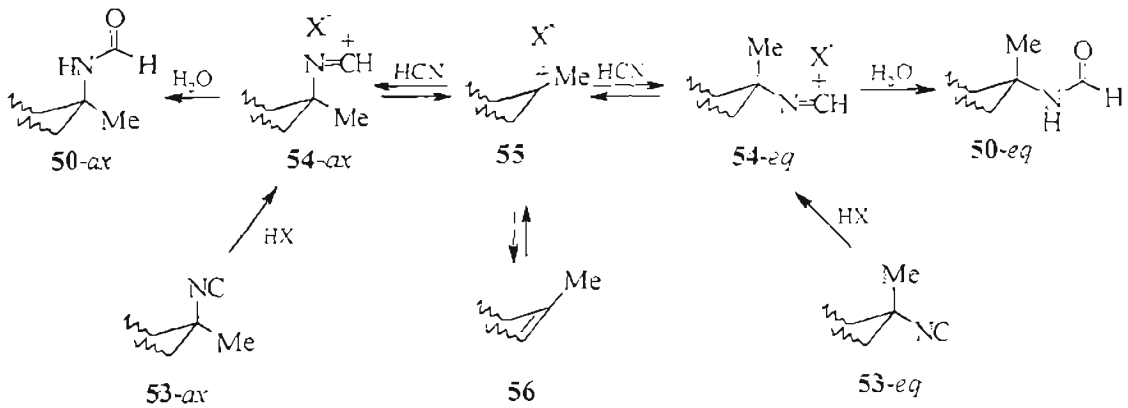
25. shēma

8. tabula Diastereomēro **50**-*ax* un **50**-*eq* amīdu attiecība, protonējot izonitrilus **53**-*ax* un **53**-*eq* Ritera reakcijas apstākļos

Izonitrils	Reakcijas laiks	**50**-*ax* : **50**-*eq*
53-*eq*	1min	52 : 48
	10 min	56 : 44
	1h	58 : 42
	5h	66 : 34
	23 h	65 : 35
	31 h	65 : 35
53-*ax*	10 min	93 : 7
	1h	92 : 8
	5h	94 : 6

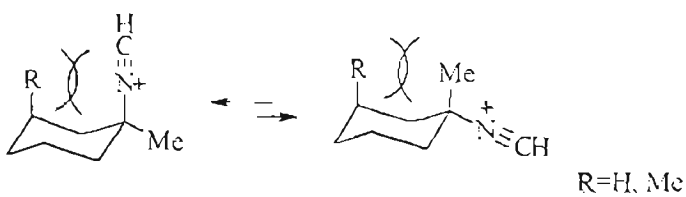
Interesanti, ka protonējot izonitrilu **53**-*eq*, ātri novērojama gandrīz ekvimolāra abu izomēro amīdu **50**-*ax* un **50**-*eq* attiecība, taču tālāk pakāpeniski pieaug aksiālā amīda **50**-*ax* pārsvars. Iespējams, ka sākumā *in situ* ģenerētais nitrīlija jons **54**-*eq* daļēji pārvēršas par amīdu **50**-*eq* un daļēji veido karbkatjonu **55**, no kura, savukārt, veidojas izomērais nitrīlija jons **54**-*ax* un cikloheksēns **56** (vai arī citi karbkatjona stabilizācijas reakcijas produkti - cikloheksanols vai sērskābes esteris). Cikloheksēns **56** ievērojami lēnāk

apgriezeniski transformējas par karbkatjonu **55**, no kura reakcijā ar zilskābi veidojas abi nitrīlija joni **54**-*ax* un **54**-*eq* kinētiskajā attiecībā, atšķirībā no reakcijas sākuma, kad lielā pārākumā bija nitrīlija jons **54**-*eq* (26. shēma).



26. shēma

Kā liecina pētījuma rezultāti, Ritera reakcijas stereoķīmisko rezultātu lielā mērā nosaka termodinamiskā kontrole. Tāpēc var secināt, ka aksiālo amīdu **49**-**52**-*ax* un d_8-**51**-*ax* veidošanās pārsvaru cikloalkanolu **3a**-*ax*, **40**-*ax*, **40**-*eq*, **3f**-*ax*, d_8-**3f**-*ax* un **48** Ritera reakcijā (18-22. shēmas) nosaka aksiālā nitrīlija jona augstāka termodinamiskā stabilitāte salīdzinājumā ar ekvatoriālo nitrīlija jonu. Tas, vistīcamāk, izskaidrojams ar nitrīlija grupas mazāku 1,3-diaksiālo sadarbību, salīdzinot ar telpiski lielāko metilgrupu (14. attēls).

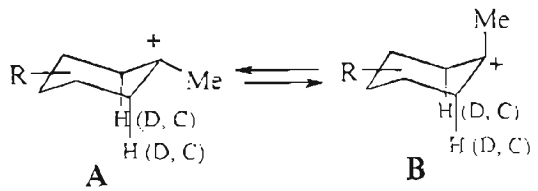


14. attēls

Neskatoties uz stēriski ļoti līdzīgo apkārtni karbkatjonos, kuri Ritera reakcijā tika ģenerēti *in situ* no cikloalkanoliem **3f**-*ax*, d_8-**3f**-*ax* un **48**, iegūto amīdu **51**-*ax*-*eq*, d_8-**51**-*ax*,*eq*, **52**-*ax*,*eq* attiecība ievērojami atšķiras (20-22. shēmas).

Saskaņā ar jaunākajiem pētījumiem cikliskie karbkatjoni eksistē kā divi savstarpēji invertējoši izomēri **A** un **B** ar piramidālu aizvietotāju novietojumu ap lādētu C-atomu (15. attēls). Tiek uzskatīts, ka izomēru attiecību nosaka karbkatjona p-orbitāles hiperkonjugācija ar antiperiplanārajām β-saišu saistošajām orbitālēm.[51,52] Tā kā C-D un C-C saites ir vājāki elektrondonori, salīdzinot ar C-H saiti,[51] jāsecina ka karbkatjonos, kas

ģenerēti no cikloalkanoliem $\mathbf{d_8}$-**3f**-*ax* un **48**, izomērs **B** ir vairāk apdzīvots kā katjonā, kas ģenerēts no cikloheksanola **3f**-*ax* (no literatūras[31] zināms, ka β-protonu aizvietošana ar deitērijiem 1-metilcikloheksilkatjonā palielina izomēra **B** populāciju 4-5×, savukārt salīdzinoši dati par 1,3,3,5-trimetilcikloheksil un 2,4,4-trimetiladamantilkatjoniem nav pieejami).



15. attēls

Pieņemot, ka nukleofīla uzbrukuma virzienu ietekmē ne tikai aizvietotāju stēriskais efekts, bet arī izomēru **A** un **B** populācija, nitrila uzbrukums no ekvatoriālās puses katjoniem, kas ģenerēti no cikloalkanoliem $\mathbf{d_8}$-**3f**-*ax* un **48**, var notikt vieglāk kā katjonam, kas ģenerēts no cikloheksanola **3f**-*ax*. Ņemot vērā, ka termodinamiskā kontrole Ritera reakcijā nav pilnīga, iespējams, atšķirīgā nitrīlija jonu veidošanās kinētiskā attiecība ir cēlonis atšķirīgai amīdu **51**-*ax*-*eq*, $\mathbf{d_8}$-**51**-*ax*,*eq* un **52**-*ax*,*eq* attiecībai.

6. 1,3,3,5,5-Pentametilcikloheksānamīna liela apjoma sintēzes metodes izstrādāšana

No visiem šajā darbā sintezētajiem amīniem - potenciāliem N-metil-D-aspartāta (NMDA) receptora fenciklidīna (PCP) saistīšanās vietas ligandiem 1,3.3,5.5-pentametilcikloheksānamīns (**5k**) uzrādīja visaugstāko receptora afinitāti *in vitro* (sk. 7. nodaļu) un daudzsološas farmakoloģiskās īpašības *in vivo*.[22] Tāpēc, lai veiktu padziļinātus pētījumus, bija jāizstrādā metode šī savienojuma liela apjoma sintēzei. 1,3,3,5,5-Pentametilcikloheksanolu (**3k**), kas nepieciešams amīna **5k** sintēzei, var viegli iegūt no komerciāli pieejamā un lētā izoforona **2k** (sk. 2. nodaļu) divās stadijās, kas no tehnoloģiskā viedokļa grūtības nerada. Noteicošā stadija amīna **5k** iegūšanā ir aminofunkcijas ievadīšana. Lai gan azidēšanas reakcija 1,3.5-aizvietoto cikloheksilamīnu sintēzē deva labus rezultātus (2. nodaļa), tomēr šī metode slāpekļūdeņražskābes eksplozīvo īpašību dēļ ir piemērota tikai nelielu vielas daudzumu iegūšanai. Tāpēc pētījumus koncetrējām uz Ritera reakciju[43] kā iespējamo tehnoloģisko risinājumu aminofunkcijas ievadīšanai pie trešējā oglekļa atoma.

Terc-karbīnamīnu iegūšanai visplašāk tiek izmantota Ritera reakcija ar HCN, jo formilgrupu Ritera reakcijā iegūtajos formamīdos var viegli nošķelt gan bāziskajā, gan skābajā hidrolīzē.[43,53,54] Samērā nesen aprakstīta formamīdu iegūšana, kā nitrila komponenti izmantojot trimetilsilicianīdu (TMSCN).[42] Publikācijas autori uzskata, ka TMSCN ir nukleofīls HCN ekvivalents, un atsevišķos piemēros demonstrē TMSCN efektivitāti salīdzinājumā ar HCN.

1,3,3,5,5-Pentametilcikloheksanola (**3k**) Ritera reakcijā ar TMSCN ieguvām vēlamo formamīdu **13a** ar augstu iznākumu (27. shēma, 9. tabula). Formamīdu **13a** hidrolizējām skābā vidē un izdalījām 1,3,3,5.5-pentametilcikloheksilamīnu (**5k**) (27. shēma, 9. tabula). Amīna **5k** iegūšanu no spirta **3k** var realizēt, neizdalot formamīdu **13a** no reakcijas maisījuma. Šajā gadījumā amīna **5k** kopējais iznākums bija 88%.

Lai gan Rittera reakcijā ar TMSCN sasniedzām vēlamo rezultātu, tomēr, likās apšaubāmi, ka TMSCN spēj izturēt skābos reakcijas apstākļus un darbojas kā nitrila komponente. ^{1}H-NMR eksperiments parādīja, ka TMSCN sāk sadalīties tiklīdz tā šķīdumam $CDCl_3$ pievieno dažus pilienus etiķskābes. Tas liecina, ka TMSCN Ritera reakcijas apstākļos (H_2SO_4/ AcOH) nitrila komponente ir zilskābe (HCN). Zilskābe, ko

ģenerējām *in situ* no kālija cianīda (KCN) cikloheksanola **3k** Ritera reakcijā izrādījās līdzvērtīgi efektīva (27. shēma, 9. tabula).

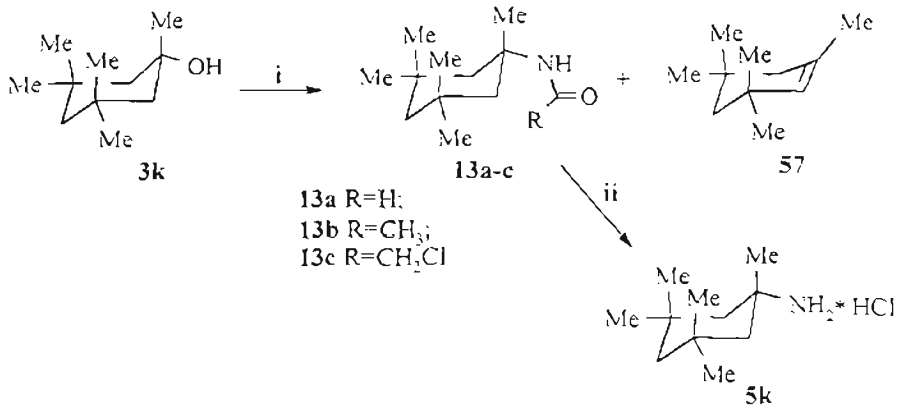
Būtisks trūkums tehnoloģiskai TMSCN un KCN izmantošanai Ritera reakcijā ir ļoti toksiskās HCN veidošanās skābajos reakcijas apstākļos. Tāpēc kā alternatīvu aminofunkcijas ievadīšanai mēģinājām izmantot cikloheksanola **3k** Ritera reakciju ar acetonitrilu (CH_3CN). No literatūras zināms, ka 1-metilcikloheksanols Ritera reakcijā ar CH_3CN sērskābes klātbūtnē ar labu iznākumu veido N-acetil-1-metilcikloheksānamīnu.[55] Līdzīgos reakcijas apstākļos no 1,3,3,5,5-pentametilcikloheksanola (**3k**) kā galveno reakcijas produktu ieguvām 1,3,3,5,5-pentametilcikloheksēnu (**57**) (27. shēma, 9. tabula) un, ar ļoti zemu iznākumu, vēlamo acetamīdu **13b**. Reakcijas temperatūras paaugstināšana acetamīda **13b** iznākumu būtiski neietekmēja (9. tabula), taču veicināja blakus produktu veidošanos.

Sistemātiski variējot reakcijas apstākļus (skābes, temperatūru un reaģentu attiecību), noskaidrojām, ka cikloheksanola **3k** reakcijā ar acetonitrilu var iegūt vēlamo acetamīdu ar labu iznākumu tad, ja kā reakcijas vidi izmanto kūpošo slāpekļskābi (9. tabula). Tomēr, jāatzīmē, ka izmantojot zemākas kvalitātes slāpekļskābi, atsevišķos gadījumos norisinājās spontāna oksidēšanās reakcija ar slāpekļa oksīdu izdalīšanos.

Vismaigākie apstākļi N-acetil-*terc*-karbīnamīnu acetilgrupas nošķelšanai ir divstadiju process, kas ietver acetamīda O-alkilēšanu ar trietiloksonija tetrafluorborātu,[56] Tomēr šī metode nav izmantojama vielu iegūšanai lielos daudzumos trietiloksonija tetrafluorborāta augstās cenas dēļ.

N-Acetil-*terc*-karbīnamīnu hidrolīzi iespējams realizēt tikai bāziskos apstākļos, paaugstinātā temperatūrā.[57,58] Skābajā hidrolīzē, atšķirībā no N-formil-*terc*-karbīnamīniem, ar N-acetil-*terc*-karbīnamīniem notiek retro-Ritera reakcija.[59] No visiem acetamīda **13b** hidrolīzes mēģinājumiem visaugstāko amīna **5k** iznākumu sasniedzām, acetilgrupu šķeļot ar kālija hidroksīdu vārošā n-oktanolā (27. shēma, 9. tabula).

Ņemot vērā grūtības, kas saistītas ar acetamīda **13b** sintēzi un acetilgrupas nošķelšanai nepieciešamos smagos hidrolīzes apstākļus, atteicāmies no šīs pieejas tālākas optimizēšanas.



Reakcijas apstākļi. i: Ritera reakcija, sk. 9. tabulu 1; ii: acilgrupas nošķelšana, sk. 10. tabulu

27. shēma

9. tabula Cikloheksanola **3k** Ritera reakcija

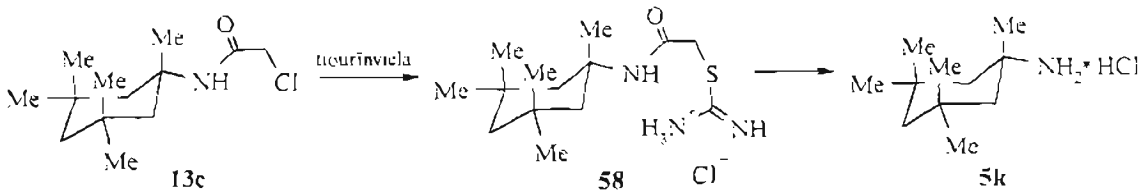
Npk.	Reakcijas apstākļi	R-jas produkts (iznākums, %)
1	TMSCN, H_2SO_4, AcOH, i.t., 15 h	**13a** (78)
2	KCN, H_2SO_4, AcOH, i.t., 15 h	**13a** (86)
3	CH_3CN, H_2SO_4, AcOH, i.t., 21 h	**13b** (3); **57** (45)
4	CH_3CN, H_2SO_4, 50-60°C, 4 h	**13b** (15)
5	CH_3CN, HNO_3, 50-60°C, 4 h	**13b** (60)
6	CH_2ClCN, H_2SO_4, AcOH, i.t., 5 h	**13c** (95)

10. tabula Acilgrupas nošķelšana amīdos 13a-c

Npk.	Amīds	Reakcijas apstākļi	Iznākums, %
1	**13a**	1) 20% H_2SO_4, 100°C, 4 h 2) HCl	66
2	**13b**	1) oktanols, KOH, 196°C, 10 h 2) HCl	81
3	**13c**	1) EtOH-AcOH, 5:1, tiourīnviela, 78°C, 17 h 2) HCl	89

Tā kā hloracetilgrupu amīdos var nošķelt ar tiourīnvielu,[60-62] amīna **5k** iegūšanai mēģinājām izmantot hloracetamīdu **13c**. No literatūras ir zināmi vairāki piemēri *N-terc*-alkilhloracetamīdu sintēzei no trešējiem spirtiem Ritera reakcijā ar hloracetonitrilu ($ClCH_2CN$).[44] Ritera reakcijas apstākļos no spirta **3k** un $ClCH_2CN$ ar augstu iznākumu ieguvām hloracetamīdu **13c** (9. tabula). Amīda **13c** hloracetilgrupas nošķelšanu kontrolējām ar plānslāņa hromatogrāfijas metodi. Hloracetamīds **13c** ātri reaģē ar tiourīnvielu, veidojot izotiouronija sāli **58**, kas lēni sadalās par amīnu **5k**. Tāpēc, analizējot reakcijas gaitu, kā standartu izmantojām izotiouronija sāli **58**.

Tradicionālajos hloracetilgrupas nošķelšanas apstākļos (vārošā etanolā), amīna **5k** veidošanās bija ļoti lēna (pēc 17 h vārīšanas amīna **5k** iznākums bija 30%). Tas, iespējams, izskaidrojams ar to, ka amidogrupa savienojumā **13c** ir stēriski vairāk traucēta kā mazāk sazarotajos otrējos un trešējos amīdos.[57-59] Eksperimentāli noskaidrojām, ka izotiouronija sāls **58** sadalīšanās ātrums ir atkarīgs no etiķskābes koncentrācijas reakcijas maisījumā (10. tabula). Kā optimālos reakcijas apstākļus amīda **13c** hloracetilgrupas nošķelšanai ar tiourīnvielu izvēlējāmies etanola un etiķskābes maisījumu (5:1), vārot 10 h (iznākums pēc 10 h (10. tabula) praktiski neatšķiras no iznākuma pēc 7 h vārīšanas (11. tabula)).



28. shēma

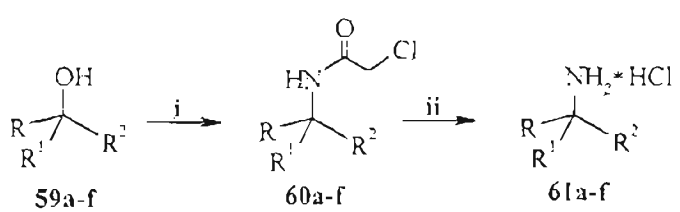
11. tabula Reakcijas apstākļu optimizēšana amīda **13c** hloracetilgrupas nošķelšanai

N pk.	EtOH/AcOH attiecība	**58** pilnīga izzušana, h	**5k** iznākums, %
1	20:1	18	81
2	10:1	11	85
3	5:1	7	88

Augstie iznākumi gan cikloheksanola **3k** Ritera reakcijā, gan hloracetilgrupas nošķelšanas stadijā, ļauj izmantot šo pieeju amīna **5k** liela apjoma sintēzei, un tā dod iespēju izvairīties no toksiskiem un dārgiem reaģentiem.

6.1. *terc*-Karbīnamīnu iegūšana, izmantojot Ritera reakciju ar hloracetonitrilu

Iepriekšējā nodaļā parādījām, ka efektīva metode 1,3,3,5,5-pentametilcikloheksilamīna (**5k**) sintēzei ir cikloheksanola **3k** Ritera reakcija ar hloracetonitrilu un sekojoša amīda **13c** hloracetilgrupas nošķelšana ar tiourīnvielu. Ņemot vērā, ka šī ir jauna piecja aminofunkcijas ievadīšanai pie trešējā oglekļa atoma, plašāk pētījām tās izmantošanas iespējas strukturāli atšķirīgu trešējo spirtu **59a-f** pārvēršanai par *terc*-karbīnamīniem **61a-f** (29. shēma, 12. tabula).

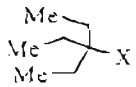
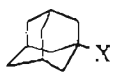
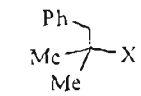
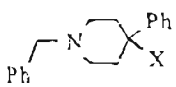
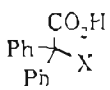
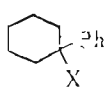


59a-f **60a-f** **61a-f**

Reakcijas apstākļi. i: $ClCH_2CN$, H_2SO_4, AcOH, 5h, i.t.; ii: tiourīnviela, EtOH/AcOH (5:1), vār. 10 h.

29. shēma

12. tabula Hloracetamīdu **58** un amīnu **59** iznākumi

Npk.	RR^1R^2CX	**60** (X=NHCOCH$_2$Cl) iznākums, %	**61** (X=NH$_3^+$Cl$^-$) iznākums, %
1		**60a**, 84	**61a**, 80
2		**60b**, 95	**61b**, 85
3		**60c**, 78	**61c**, 84
4		**60d**, 73	**61d**, 74
5		**60e**, 91	**61e**, 61
6		**60f**, -	**61f**, -

*Dihidrohlorīds ir ļoti higroskopisks, tāpēc amīns **61d** tika izdalīts brīvas bāzes veidā.

Spirtu **59a-f** Ritera reakcijā ar $ClCH_2CN$ ieguvām hloracetamīdus **60a-e** ar labiem iznākumiem. 1-Fenilcikloheksanola (**59f**) gadījumā vēlamais amīds **60f** neradās un kā galveno produktu no reakcijas izdalījām 1-fenilcikloheksēnu. No literatūras zināms, ka 1-fenilcikloheksanols **59f** Ritera reakcijā ar PhCN un HCN dod atbilstošos amīdus ar ļoti zemiem iznākumiem.[63] Tas, iespējams, saistīts ar 1-fenilcikloheksilkatjona zemo elektrofilitāti. Jāatzīmē, ka tā heteroanalogs 4-fenilpiperidīn-4-ols **59d** efektīvi reaģē ar CH_3CN[64] un, kā mēs parliecinājāmies, arī ar $ClCH_2CN$ (12. tabula).

Amīdu **60a-e** hloracetilgrupas nošķelšanai izmantojām eksperimentos ar N-hloracetil-1,3,3,5,5-pentametilcikloheksilamīnu optimizētos reakcijas apstākļus (sk. 5. nodaļu) un ieguvām *terc*-karbīnamīnus **61a-e** ar labiem iznākumiem (29. shēma, 12. tabula).

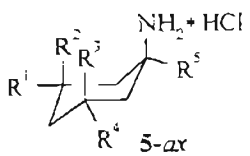
7. Karbociklisko amīnu NMDA receptora saistības afinitāte

2-4. Nodaļās aprakstīto sintezēto karbociklisko amīnu NMDA receptora PCP saistīšanās vietas affinitāte tika noteikta ar radioliganda ([^{3}H]MK-801) izspiešanas metodi žurku smadzeņu paraugos.[22] 1,3,5-Aizvietoto cikloheksānamīnu **5a-p**, 1,3,3,5,5-pentametilcikloheksānamīna N-alkilatvasinājumu **10a-c** un 1-(aminoalkil)-3,3,5,5-tetrametilcikloheksānu **11a-c** receptora saistības affinitātes (K_i) apkopotas 13-15. tabulās. Salīdzinājumam dota amantadīna un memantīna receptora saistības afinitāte. Bioķīmiskie dati par 1-azaspiro-dekānu **12a** un undekānu **12b** promocijas darba noformēšanas laikā vēl nebija pieejami. 1,3,5,7-Tetrametilbiciklo[3.3.1]nonān-3-amīna **29a**-*ax* NMDA receptora saistības affinitāte ir 54 μM.

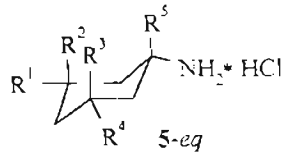
Detalizēta sintezēto savienojumu biofizikālo parametru un terapeitiskā profila analīze veikta sadarbības partneru zinātniskajā publikācijā.[22]

No promocijas darbā sintezētajiem karbocikliskajiem amīniem memantīnam līdzīgu afinitāti (13,14 tabula), receptora bloķēšanas/debloķēšanas kinētiku un afinitātes atkarību no membrānas potenciāla[22] uzrādīja savienojumi **5i**-*ax,eq*, **5k,l,n**, **10a,b** un **11b**. *In vivo* pētījumos ar pelēm šie savienojumi uzrādīja arī augstu aktivitāti pret maksimālā elektrošoka inducētām konvulsijām, ko visticamāk nodrošina NMDA receptora antagonizēšana.[22] No sintezētā savienojumu klāsta visaugstākā NMDA receptora affinitāte piemīt 1,3,3,5,5-pentametilcikloheksānamīnam (**5k**). Būtiski, ka amīns **5k** atšķirībā no tā homologiem, kuriem piemīt līdzīgas biofizikālās īpašības, ir simetrisks, un tā sintēze ietver vismazāko stadiju skaitu. Tāpēc 1,3,3,5,5-pentametilcikloheksānamīns tika izraudzīts kā preparāta kandidāts dažādu CNS disfunkciju ārstēšanai un pašlaik iziet pirmās fāzes klīniskos pētījumus

13. tabula 1,3,5-Aizvietoto cikloheksānamīnu NMDA receptora saistības afinitāte



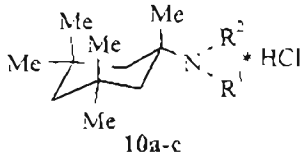
5-*ax*



5-*eq*

Savienojums	R^1	R^2	R^3	R^4	R^5	Ki (μM)
5a-*ax*	H	H	H	Me	Me	52,61
5a-*eq*						65,29
5b-*ax*	H	H	H	Et	Me	49.28
5b-*eq*						49,10
5c-*ax*	H	H	H	Pr	Me	70,95
5c-*eq*						49.18
5d	H	H	Me	Me	Me	32,20
5e-*ax*	Me	H	H	Me	Me	30.00
5e-*eq*						19.21
5f-*ax*	Me	H	Me	Me	Me	7,74
5f-*eq*						4,66
5g-*ax*	Me	H	Et	Me	Me	13,32
5g-*eq*						15,14
5h-*ax*	Me	H	Pr	Me	Me	24,02
5h-*eq*						57,76
5i-*ax*	Me	Me	H	Et	Me	5,18
5i-*eq*						2,88
5j-*ax*	Me	Me	H	Pr	Me	15,01
5j-*eq*						13,40
5k	Me	Me	Me	Me	Me	1,47
5l	Me	Me	Me	Me	Et	2,28
5m	Me	Me	Me	Me	Pr	8,09
5n	Me	Me	Et	Et	Me	3,16
5o	Me	Me	Pr	Pr	Me	16,48
5p	H	H	H	H	Me	144,33
Amantadīns						25,87
Memantīns						2,45

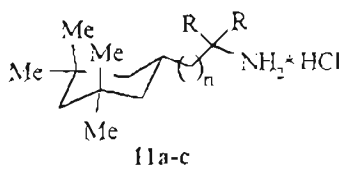
14. tabula 1,3,3,5,5-Pentametilcikloheksānamīna N-alkil atvasinājumu NMDA receptora saistības afinitāte



10a-c

Savienojums	R^1	R^2	Ki (μM)
10a	H	Me	4,83
10b	H	Et	4,17
10c	Me	Me	12,72
Amantadīns			25,87
Memantīns			2,45

15. tabula 1-(1-Aminoalkil)-3,3,5,5-tetrametilcikloheksānamīna NMDA receptora saistības afinitāte



11a-c

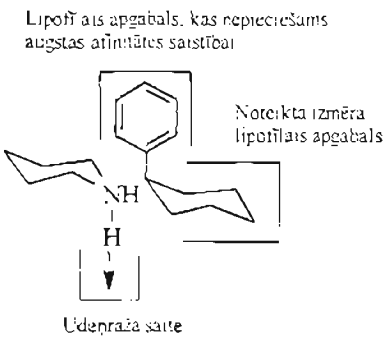
Savienojums	n	R	Ki (μM)
11a	0	H	17,84
11b	1	H	4,84
11c	1	Me	60,17
Amantadīns			25,87
Memantīns			2,45

7.1. Karbociklisko amīnu struktūras un NMDA receptora saistības afinitātes likumsakarības.

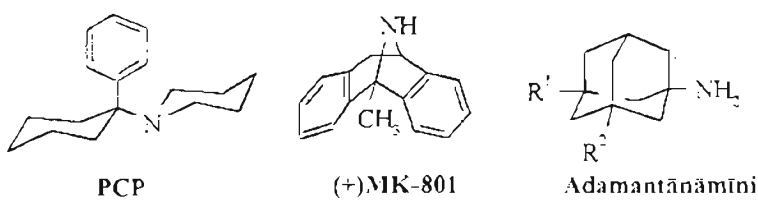
Viens no mūsu darba uzdevumiem bija noskaidrot karbociklisko amīnu lipofīlās daļas ietekmi uz NMDA receptora saistību. Šim nolūkam piemēroti ir 1,3,5-aizvietotie

cikloheksānamīni **5**, kuros aizvietotāji dod iespēju samērā plaši variēt lipofīlās globulas telpiskos izmērus.

NMDA receptora PCP saistīšanās vietas ligandu kvantitatīvās struktūras - afinitātes likumsakarības (KSAL) ir pētītas vairākām savienojumu klasēm.[65,66] Šajos pētījumos tika noskaidrots, ka PCP saistīšanās vieta ir iedobe ar noteiktiem izmēriem, un augstai ligandu afinitātei kā farmakoforie elementi nepieciešami aromātiskais gredzens un aminogrupa.[65,66] Veicot molekulāro modelēšanu, ir izveidots farmakoforais modelis, kurā parādīts, ka PCP saistīšanās vieta sastāv no protonētas aminogrupas piesaistes centra un diviem lipofīlajiem apgabaliem[66] (16. attēls). Vienā no tiem saistās augstai afinitātei nepieciešamā aromātiskā molekulas daļa, kas atbilst PCP molekulas fenilgrupai un vienam MK-801 aromātiskajam gredzenam. Otru apgabalu ieņem PCP cikloheksāna gredzens un otrs MK-801 aromātiskais gredzens. Saskaņā ar šo modeli tiek uzskatīts, ka adamantānamīnu lipofīlā daļa ieņem apgabalu, kas atbilst PCP cikloheksāna gredzenam.[66] Adamantānamīnu mērenā afinitāte tiek skaidrota ar lipofīlās daļas stērisku neatbilstību šī apgabala telpiskajiem izmēriem.



16. attēls



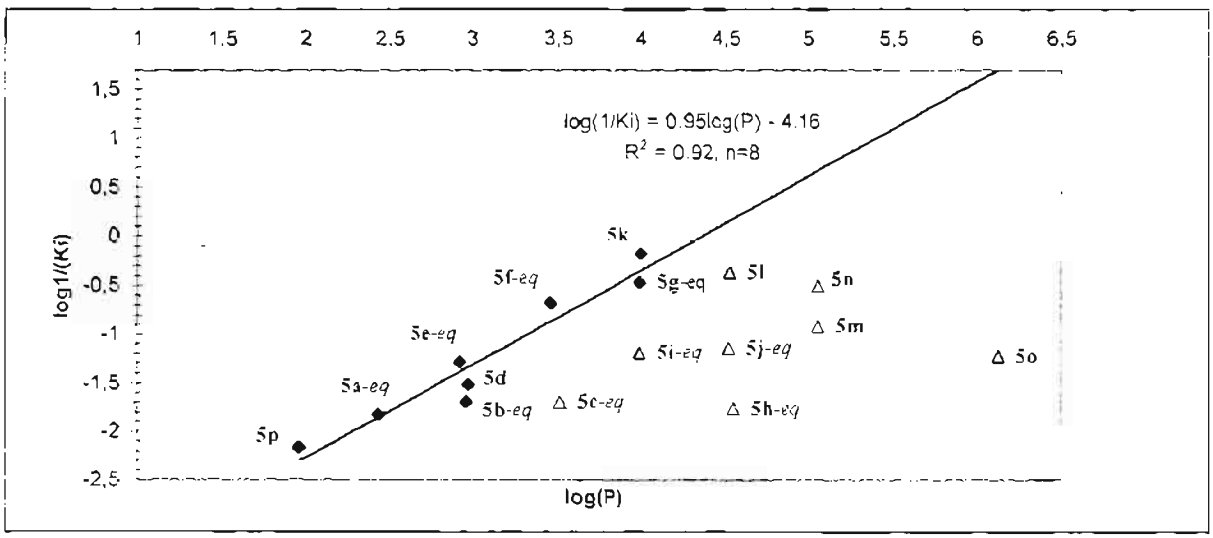
17. attēls

Cikloheksānamīni **5a-c,e-j**-*eq* un **5d,k-p**, kuriem zemākās enerģijas konformācijā aminogrupa novietota ekvatoriāli, ir vistuvākie adamantānamīnu struktūranalogi. Šie amīni savstarpēji atšķiras ar telpiskajiem izmēriem un lipofilitāti, tāpēc to KSAL noskaidrošanai piemērota Hanša analīze.[67] Hanša vienādojums (1) izsaka savienojumu saistīšanās afinitāti kā funkciju no logP (hidrofobā efekta deskriptors) un log (S) (stēriskais deskriptors).

$$\log (1/K) = a \log (P) + b \log (S) + c \quad (1)$$

Hidrofobā efekta deskriptous logP (16. tabula) cikloheksānamīniem **5a-c,e-j**-*eq* un **5d,k-p** aprēķinājām, integrējot fragmentu lipofilitātes konstantes[68] ar datorprogramu ACD/LogP 1.0.

Kā redzams no 18. attēla, cikloheksānamīniem **5a,b,e-g**-*eq* un **5d,k,p** (♦) afinitāte, kas izteikta kā log (1/K_i) (16. tabula) ir lineāra funkcija no to lipofilitātes (log(P)). Tas nozīmē, ka stēriskais deskriptorus ir nenozīmīgs, respektīvi, šie savienojumi pēc tepiskajiem izmēriem atbilst PCP saistīšanās vietai. Apjomīgāku amīnu **5c,h-j**-*eq* un **5l-o** (Δ) gadījumā vērojama izteikta novirzīšanās no liniaritātes, kas norāda, ka to saistību būtiski ietekmē stēriskais faktors.



18. attēls

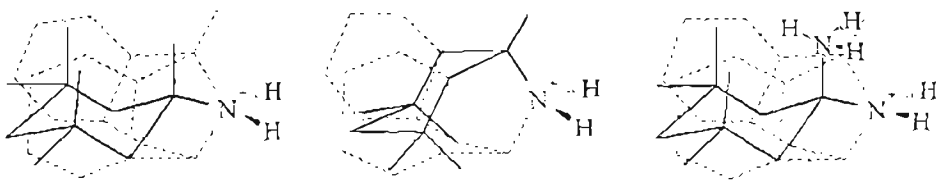
16. tabula 1,3,5-Aizvietoto cikloheksānamīnu log(1/Ki). un log(P) lielumi

Savienojums	log (1/Ki)	log (P)	Savienojums	log (1/Ki)	log (P)
2a-*eq*	-1,82	2,43	**2i**-*eq*	-0,46	3,99
2b-*eq*	-1,69	2,96	**2j**-*eq*	-1,13	4,52
2c-*eq*	-1,69	3,49	**2k**	-0,17	4,00
2d	-1,57	2,97	**2l**	-0,36	4,53
2e-*eq*	-1,28	2,92	**2m**	-0,91	5,06
2f-*eq*	-0,67	3,46	**2n**	-0,50	5,06
2g-*eq*	-1,18	3,99	**2o**	-1,22	6,13
2h-*eq*	-1,76	4,52	**2p**	-2,16	1,94

Interesanti, ka veicot Hanša analīzi kopā ar konformacionāli ierobežotajiem amīniem **5a,b,e-g**-*eq*, ļoti precīca korelācija realizējas arī simetrisko cikloheksānamīnu **5d,k,p** gadījumā, kaut arī abas šo savienojumu konformācijas ir līdzīgi apdzīvotas. To var

izskaidrot, ja pieņem, ka abi konformēri ar receptoru saistās līdzvērtīgi, uz ko norāda ļoti līdzīgās konformacionāli ierobežoto cikloheksānamīnu **5**-*ax* un **5**-*eq* afinitātes (13. tabula).

Pēc Hanša analīzes veikšanas cikloheksānamīnus **5a-c,e-j**-*eq* un **5d,5k-p** savietojām ar vienu no augstas afīnitātes PCP saistīšanās vietas ligandiem (+)MK-801 (19a. attēls), izvēloties slāpekļa atomu kā kopējo punktu. Būtiski, ka amīni **5a,b,e-g**-*eq* un **5d,5k,p**, kuri Hanša analīzē uzrādīja stērisku atbilstību PCP saistīšanās vietai, ievietojas telpā starp MK-801 aromātiskajiem gredzeniem. Savukārt, amīni **5c,h-j**-*eq* un **5l-o**, kuru saistību ar receptoru ietekmē stēriskais faktors (aksiālie aizvietotāji lielāki par metilgrupu un ekvatoriālie aizvietotāji lielāki par etilgrupu), ievērojami pārsniedz MK-801 dimensijas. No tā izriet nozīmīgs secinājums, ka 1,3,5-aizvietoto cikloheksānamīnu **5**, un līdz ar to arī adamantān-1-amīnu lipofīlā daļa neiekļaujas noteiktā farmakoforā modeļa lipofīlajā apgabalā (16. attēls), bet gan atpazīst PCP saistīšanās vietu ka vienotu hidrofobo reģionu. PCP saistīšanās vietai stēriski atbilstīgo cikloheksānamīnu **5** un adamantānamīnu mēreno afinitāti drīzāk var izskaidrot ar svarīga farmakoforā elementa - aromātiskās sistēmas, kas nepieciešama augstai afinitātei, trūkumu.



19. attēls

Konformacionāli ierobežoto 1,3,5-aizvietoto cikloheksānamīnu izomēru **5**-*ax* un **5**-*eq* līdzīgo afinitāti (13. tabula) var skaidrot divejādi. Ja cikloheksānamīnu izomērus **5**-*ax* savieto ar (+)MK-801, izraugoties slāpekļa atomu kā kopējo punktu, lipofīlā daļa iekļaujas MK-801 dimensijās tikai tad, ja aksiālie aizvietotāji nav lielāki par metilgrupu un ekvatoriālie aizvietotāji nav lielāki par etilgrupu (19b attēls). No tā izriet, ka stēriskie ierobežojumi amīnu **5**-*ax* receptora saistībai ir līdzīgi kā to izomēriem **5**-*eq*.

Nevar izslēgt, ka aksiālajai aminogrupai cikloheksānamīnu izomēros **5**-*ax* atbilst cits piesaistes punkts nekā to izomēriem **5**-*eq*. Ja cikloheksānamīnus **5**-*ax* savieto ar (+)MK-801 tādā pašā veidā, kā to izomērus **5**-*eq* (19c attēls), aminogrupa cikloheksānamīnos **5**-*ax* ir novietota tuvu MK-801 5. pozīcijas metilgrupai. MK-801 radniecīgo savienojumu SAL pētījumi liecina, ka MK-801 5. pozīcijas metilgrupas tuvumā, iespējams, atrodas cits piesaistes punkts, kas spēj veidot ūdeņraža saiti.[69]

8. Secinājumi

1. Attīstītas 1,3,5-aizvietoto cikloheksānamīnu sintēzes metodes. Izmantojot trešējo spirtu azidēšanas reakciju un diastereomēro azidocikloheksānu hromatogrāfisko dalīšanu, iegūti nesimetriski 1,3,5-aizvietoto cikloheksānamīnu konformacionāli ierobežoti diastereomēri ar fiksētu *ax*- un *eq*-aminogrupu.

2. Sintezēti 1,3,3,5,5-pentametilcikloheksānamīna struktūranalogi - N-alkil-1,3,3,5,5-pentametilcikloheksānamīni, 1-aminoalkil-3,3,5,5-tetrametilcikloheksānamīni, kā arī 7,7,9,9-tetrametil-1-azaspiro[4.5]dekāns un 8,8,10,10-tetrametil-1-azaspiro[5.5]undekāns.

3. Izstrādāta jauna, vispārīga pieeja 1-azaspirociklisko savienojumu iegūšanai no cikloalkanoniem. Azacikla saslēgšanu izdara, laktamizējot 1-amino-1-(ω-karboksialkil)cikloalkānu, kura aminofunkciju ievada Ritera reakcijā, bet kā karboksilfunkcijas latento grupu izmanto fenilgrupu.

4. Sintezēts 1,3,5,7α-tetrametilbiciklo[3.3.1]nonān-3α-amīns. Noskaidrots, ka aminofunkcijas ievadīšana biciklo[3.3.1]nonāna 3-pozīcijā, izmantojot Ritera reakciju ar TMSCN, notiek *endo*-selektīvi.

5. Izpētītas 1-metilcikloheksanolu Ritera reakcijas diastereoselektivitātes likumsakarības. Neatkarīgi no karbkatjona stēriskās apkārtnes ar lielu pārsvaru veidojas *ax*-amīda izomērs. Pierādīts, ka Ritera reakcijas apstākļos notiek starpproduktu - diastereomēro nitrīlija jonu epimerizēšanās. Tas norāda, ka amīdu veidošanās diastereoselektivitāte Ritera reakcijā tiek kontrolēta pārsvarā termodinamiski.

6. 1,3,3,5,5-Pentametilcikloheksānamīna sintēzes noteicošā posma izstrādāšanai pētīta 1,3,3,5,5-pentametilcikloheksanola Ritera reakcija ar TMSCN, HCN, CH_3CN un $ClCH_2CN$. Atrasts, ka Ritera reakcija ar $ClCH_2CN$ un sekojoša hloracetilgrupas nošķelšana ar tiourīnvielu ir efektīva aminofunkcijas ievadīšanas metode, kas ļauj izvairīties no toksiskiem un dārgiem reaģentiem, kā arī smagiem reakcijas apstākļiem. Šīs jaunās pieejas iespējas nodemonstrētas arī citu, strukturāli atšķirīgu *terc*-karbīnamīnu iegūšanai.

7. Veikta 1,3,5-aizvietoto cikloheksānamīnu lipofilitātes un NMDA receptora afinitātes korelāciju (Hanča) analīze. Noskaidrots, ka karbociklisko amīnu lipofīlā daļa neiekļaujas noteiktā PCP saistīšanās vietas farmakoforā modeļa hidrofobajā apgabalā, bet atpazīst šo saistīšanās vietu kā vienotu hidrofobo apgabalu. Cikloheksānamīnu lipofīlā daļa nepārsniedz PCP saistīšanās vietas telpiskos apmērus, ja 3,5-aksiālie aizvietotāji nav lielāki par metilgrupu un 3,5-ekvatoriālie aizvietotāji nav lielāki par etilgrupu.

9. Eksperimentālā daļa

Kušanas punkti noteikti kapilāros Gallenkamp aparātā un nav koriģēti. IS spektri uzņemti uz Perkin-Elmer 580B spektrometra.. ^{1}H-KMR spektri uzņemti uz Varian Mercury 200BB spektrometra. Reakciju maisījumi analizēti un produktu tīrība noteikta gāzu hromatogrāfiskajā analīzē (MN-OV-1, 25mx0,53mm, d_f= 1.0 μ, 50-270^{0}C (10^{0}C min^{-1})). Preparatīvā hromatogrāfija veikta izmantojot Kieselgelu 63-100μ. PSH analīzes veiktas uz Kieselgel 60 F_{254} plāksnītēm; eluents: heksāns-etilacetāts (dažādas attiecības); attīstīšanai izmantoti joda tvaiki. Visi eksperimentālajā daļā izmantotie reaģenti iegādāti no Aldrich. Šķīdinātāji un reaģenti sagatavoti kā aprakstīts literatūrā.[70]

Sekojošu savienojumu sintēze un fizikāli ķīmiskās īpašības dotas pielikumos: **1-9** (1. pielikums); **10,11,13a,b,14-21** (2. pielikums); **29-37** (3. pielikums); **13c,58-61** (4. pielikums). Eksperimentālajā daļā ietverta tikai literatūrā (ieskaitot pielikumā dotās publikācijas un patentus) neaprakstīto savienojumu iegūšana.

1-(2-Feniletil)-3,3,5,5-tetrametilcikloheksanols (**22a**) un 1-(3-fenilpropil)-3,3,5,5-tetrametilcikloheksanols (**22b**)

Pie 0.85 M fenilalkilmagnija bromīda (2-feniletilmagnija bromīds cikloheksanola **22a** iegūšanai un 3-fenilpropilmagnija bromīds cikloheksanola **22b** iegūšanai) šķīduma ēterī (25 ml; 20 mmol), kas atdzesēts līdz 0^{0}C, piepilina 3,3,5,5-tetrametilcikloheksanona **2k** (1,54 g; 10 mmol) šķīdumu ēterī (10 ml). Pēc 0,5 h maisīšanas uzmanīgi piepilina pies. NH_4Cl ūdens šķīdumu (30 ml). Atdala organisko fāzi un ūdens fāzi ekstrahē ar ēteri (2×20 ml). Apvienotos ekstraktus mazgā ar pies. NaCl šķīdumu un žāvē virs $MgSO_4$. Pēc šķīdinātāja aizvaicēšanas atlikumu attīra uz silikagela kolonas (80 cm^3), eluējot ar petrolētera-EtOAc (10:1) maisījumu.

Iegūst **22a** (2.1g; 82%) eļļas veidā; ^{1}H-KMR ($CDCl_3$, TMS) δ: 0,91 (6H, s, 3,5-CH_3); 1,23 (6H, s, 3,5-CH_3); 1,0-1,6 (7H, m, cikla protoni un OH); 1,6-1,8 (2H, m, $PhCH_2\underline{CH_2}$); 2,6-2,8 (2H, m, $Ph\underline{CH_2}CH_2$) un 7,0-7,4 m.d. (5H, m, Ph);

22b (2,48 g; 90%) eļļas veidā; ^{1}H-KMR ($CDCl_3$, TMS) δ: 0,86 (6H, s, 3,5-CH_3); 1,19 (6H, s, 3,5-CH_3); 1,0-1,8 (11H, m, cikla protoni, OH un $PhCH_2\underline{CH_2}CH_2$); 2,60 (2H, t, J= 7,5 Hz, $PhCH_2CH_2\underline{CH_2}$) un 7,1-7,4 m.d. (5H, m, Ph).

N-Formil-1-(2-feniletil)-3,3,5,5-tetrametilcikloheksānamīns (**23a**)

Pie cikloheksanola **22a** (0,5 g; 2 mmol), trimetilsililcianīda (0.54 ml; 4 mmol) un etiķskābes (0,32 ml) maisījuma, kas atdzesēts līdz 0°C piepilina sērskābi (0,32 ml; 6 mmol). Sērskābi pievieno ~5 min laikā, uzturot reakcijas maisījuma temperatūru zem +5°C. Pēc 23 h reakcijas maisījumu izlej ledus ūdenī (20 ml) un neitralizē ar 20% NaOH ūdens šķīdumu. Reakcijas produktu no ūdens fāzes ekstrahē ar ēteri (3×20 ml). Apvienotos ekstraktus mazgā ar pies. NaCl šķīdumu un žāvē virs $MgSO_4$. Pēc ētera aiztvaicēšanas atlikumu attīra uz silikagela kolonas (50 cm^3), eluējot ar petrolētera-EtOAc (4:1; 2:1) maisījumu.

Iegūst **23a** (0,47 g; 85%) ar k.t. 90-92° C; ^{1}H-KMR ($CDCl_3$, TMS) δ: 0,93 un 0,95 (kopā 6H, abi s, 3,5- CH_3); 1,17 un 1,19 (kopā 6H, abi s, 3,5-CH_3); 1,0-2,3 (9H, m, cikla protoni, OH un $PhCH_2\underline{CH_2}$); 2,5-2,7 (2H, m, $Ph\underline{CH_2}CH_2$); 5,3 un 5,6 (kopā 1H, pl s un d (J= 12,5 Hz), NH); 7,1-7,4 (5H, m, Ph); 8,13 un 8.33 (kopā 1H, abi d, J= 2 Hz un 12,5 Hz).

N-Hloracetil-1-(2-feniletil)-3,3,5,5-tetrametilcikloheksānamīns (**25a**) un N-hloracetil-1-(3-fenilpropil)-3,3,5,5-tetrametilcikloheksānamīns (**25b**)

Pie cikloheksanola **22a** vai **22b** (2 mmol), hloracetonitrila (1.52 ml; 4 mmol) un etiķskābes (0,96 ml) maisījuma, kas atdzesēts līdz 0°C, piepilina sērskābi (0,96 ml; 18 mmol). Sērskābi pievieno ~5 min laikā, uzturot reakcijas maisījuma temperatūru zem +5°C. Pēc 48 h reakcijas maisījumu izlej ledus ūdenī (50 ml) un neitralizē ar 20% NaOH ūdens šķīdumu. Reakcijas produktu no ūdens fāzes ekstrahē ar ēteri (3×40 ml). Apvienotos ekstraktus mazgā ar pies. NaCl šķīdumu un žāvē virs $MgSO_4$. Pēc ētera aiztvaicēšanas atlikumu attīra uz silikagela kolonas (100 cm^3), eluējot ar petrolētera-EtOAc (10:1) maisījumu.

Iegūst **25a** (1,91 g; 96%) eļļas veidā; ^{1}H-KMR ($CDCl_3$, TMS) δ: 0,93 (6H, s, 3,5-CH_3); 1,17 (6H, s, 3,5-CH_3); 1,0-1,5 (4H, m, 4-CH_2, 2,6-CH); 2,0-2.2 (2H, m, $PhCH_2\underline{CH_2}$); 2,24 (2H, d, J= 14 Hz, 2,6-CH); 2,5-2,6 (2H, m, $Ph\underline{CH_2}CH_2$); 3,90 (2H, s, CH_2Cl); 6,6 (1H, pl s, NH) un 7,1-7,3 m.d. (5H, m. Ph);

un **25b** (0,77 g; 37%) ar k.t. 83-85° C; ^{1}H-KMR ($CDCl_3$, TMS) δ: 0,89 (6H, s, 3,5-CH_3); 1,13 (6H, s, 3,5-CH_3); 0,9-1,9 (8H, m, 4-CH_2, 2,6-CH un $Ph\underline{CH_2}\underline{CH_2}CH_2$); 2:15

(2H, d, J= 14,5 Hz, 2,6-CH); 2,56 (2H, t, J= 8 Hz, $PhCH_2CH_2\underline{CH_2}$); 3,93 (2H, s, CH_2Cl); 6,5 (1H, pl s, NH) un 7,1-7,4 m.d. (5H, m, Ph).

N-Hloracetil-1-(2-oksikarboniletil)-3,3,5,5-tetrametilcikloheksānamīns (**26a**) un N-hloracetil-1-(3-oksikarbonilpropil)-3,3,5,5-tetrametilcikloheksānamīns (**26b**)

Amīda **24a** vai **24b** (2 mmol), CCl_4 (8 ml), CH_3CN (8 ml), H_2O (12 ml) un $NaIO_4$ (6,5 g; 30 mmol) maisījumam pievieno RuO_2 (6 mg) un maisa istabas temperatūrā. Pēc 72 h reakcijas maisījumu filtrē un nogulsnes uz filtra mazgā ar CH_2Cl_2 (3×10 ml). No filtrāta atdala organisko fāzi. Ūdens fāzi ekstrahē ar CH_2Cl_2 (3×10 ml). Apvienotās organiskās fāzes žāvē virs $CaCl_2$. Pēc šķīdinātāja aiztvaicēšanas atlikumu attīra uz silikagela kolonas (100 cm^3), eluējot ar petrolētera-EtOAc (4:1, 2:1 un 1:1) maisījumu.

Iegūst **26a** (0,32 g; 53%) ar k.t. 130-131°C; ^{1}H-KMR ($CDCl_3$, TMS) δ: 0,92 (6H, s, 3,5-CH_3); 1,17 (6H, s, 3,5-CH_3); 1,0-1,5 (4H, m, 4-CH_2, 2,6-CH_2); 2,0-2,4 (6H, m, OC$\underline{CH_2}CH_2$, 2,6-CH); 3,97 (2H, s, CH_2Cl) un 6,6 m.d. (1H, pl s, NH);

un **26b** (0,47 g; 74%) ar k.t. 140-141°C; ^{1}H-KMR ($CDCl_3$, TMS) δ: 0,91 (6H, s, 3,5-CH_3); 1,15 (6H, s, 3,5-CH_3); 0,9-1,8 (8H, m, 4-CH_2, 2,6-CH, OC$CH_2\underline{CH_2}\underline{CH_2}$); 2,17 (2H, d, J= 14,2 Hz, 2,6-CH); 2,33 (2H, t, J= 7,2 Hz, OC$\underline{CH_2}CH_2CH_2$); 3,97 (2H, s, CH_2Cl) un 6,6 m.d. (1H, pl s, NH).

N-Hloracetil-1-(2-etoksikarboniletil)-3,3,5,5-tetrametilcikloheksānamīns (**27a**) un N-hloracetil-1-(3-etoksikarbonilpropil)-3,3,5,5-tetrametilcikloheksānamīns (**27b**)

Pie karbonskābes **25a** vai **25b** (2 mmol) šķīduma etanolā (5 ml), kas atdzesēts līdz 0°C pievieno tionilhlorīdu (0,52 ml; 9,8 mmol) un maisa 5 h istabas temperatūrā. Reakcijas maisījumu ietvaicē un atlikumu attīra uz silikagela kolonas (50 cm^3), eluējot ar petrolētera-EtOAc (6:1) maisījumu.

Iegūst **27a** (0,55 g; 82%) eļļas veidā; ^{1}H-KMR ($CDCl_3$, TMS) δ: 0,91 (6H, s, 3,5-CH_3); 1,14 (6H, s, 3,5-CH_3); 1,25 (3H, t, J= 7 Hz, $\underline{CH_3}CH_2O$); 0,8-1,6 (4H, m, 4-CH_2, 2,6-CH); 2,0-2,4 (6H, m, OC$\underline{CH_2}CH_2$, 2,6-CH); 3,95 (2H, s, CH_2Cl); 4,11 (2H, q, J= 7 Hz, $CH_3\underline{CH_2}O$) un 6,50 m.d. (1H, pl s, NH);

27b (0,68 g; 98%) eļļas veidā; ^{1}H-KMR ($CDCl_3$, TMS) δ: 0,91 (6H, s, 3,5- CH_3); 1,14 (6H, s, 3,5-CH_3); 1,25 (3H, t, J= 7 Hz, $\underline{CH_3}CH_2O$); 0,9-1,8 (4H, m, 4-CH_2, 2,6-CH,

$OCCH_2\underline{CH_2CH_2}$); 2,18 (2H, d, 15 Hz, 2,6-CH); 2,26 (2H, t, J= 8,4 Hz, $OC\underline{CH_2}CH_2CH_2$); 3,95 (2H, s, CH_2Cl); 4,13 (2H, q, J= 7 Hz, $CH_3\underline{CH_2}O$) un 6,52 m.d. (1H, pl s, NH).

2-Okso-7,7,9,9-tetrametil-1-azaspiro[4.5]dekāns (**28a**) un 2-okso-8,8,10,10-tetrametil-1-azaspiro[5.5]undekāns (**28b**)

Estera **27a** vai **27b** (1 mmol) un tiourīnvielas (1,2 mmol) šķīdumu etanola (5 ml) un etiķskābes (1 ml) maisījumā vāra 30 h. Reakcijas maisījumu atdzesē un šķīdinātājus aiztvaicē. Pievieno 10% NaOH ūdens šķīdumu un ekstrahē ar $CHCl_3$ (3×10 ml). Ekstraktu žāvē virs $CaCl_2$, šķīdinātāju aiztvaicē un produktu attīra uz silikagela kolonas (50 cm^3), eluējot ar petrolētera-EtOAc (2:1, 1:1) maisījumu.

Iegūst **28a** (0,14 g; 54%) ar k.t. 158-160° C; ^{1}H-KMR ($CDCl_3$, TMS) δ: 1,01 (12H, s, 7,9-CH_3); 1,19 (1H, d, J= 14 Hz, 8-CH); 1,27 (1H, d, J=14 Hz, 8-CH); 1,45 (4H, s, 6,10-CH_3); 2,02 (2H, t, J= 7,5 Hz, 4-CH_2); 2,36 (2H, t, J= 7,5 Hz, 3-CH_2) un 5,8 m.d. (1H, pl s, NH);

28b (0,17 g; 76%) ar k.t. 126-128° C; ^{1}H-KMR ($CDCl_3$, TMS) δ: 1,01 (6H, s, 8,10-CH_3); 1,45 (6H, s, 8,10-CH_3); 1,0-2,0 (10H, m, 4,5,7,9,11-CH_2); 2,33 (2H, t, J= 6 Hz, 4-CH_2) un 5,8 m.d. (1H, pl s, NH).

7,7,9,9-Tetrametil-1-azaspiro[4.5]dekāns (**12a**) un 8,8,10,10-tetrametil-1-azaspiro[5.5]undekāns (**12b**)

Pie 1M borāna šķīduma THF (5 ml; 5 mmol) pievieno laktāma **27a** vai **27b** (1 mmol) šķīdumu THF (5 ml) un vāra 15h. Pēc atdzesēšanas reakcijas maisījumam pievieno k. HCl līdz skābai videi un THF aiztvaicē. Atlikumam pievieno heksānu (20ml) un 20% NaOH ūdens šķīdumu. Atdala organisko fāzi un ūdens fāzi ekstrahē ar heksānu (2×10 ml). Organisko fāzi mazgā ar pies. NaCl ūdens šķīdumu (20 ml) un žāvē virs NaOH. Heksāna ekstraktam pievieno 4,8 M HCl šķīdumu ēterī (1 ml) un šķīdinātājus aiztvaicē. Sauso atlikumu izberzē ar ēteri un filtrē. Nogulsnes žāvē eksikātorā virs NaOH.

Iegūst **12a** (0,18 g; 76%) ar k.t. 220-221° C. ^{1}H-KMR ($CDCl_3$, TMS) δ: 1,01 (6H, s, 7,9-CH_3); 1,08 (6H, s, 7,9-CH_3); 1,23 (1H, d, J= 14 Hz, 8-CH); 1,35 (1H, d, J=14 Hz, 8-CH); 1,8 (4H, pl s, 6,10-CH_2); 2,0-2,2 (4H, m, 3,4-CH_2); 3,3 (2H, pl s, 2-CH_2) un 9,4 m.d. (2H, pl s, NH_2^+);

12b (0,11 g; 45%) ar k.t. 212-214° C; ^{1}H-KMR ($CDCl_3$, TMS) δ: 1,01 (6H, s, 8,10-CH_3); 1,09 (6H, s, 8,10-CH_3); 1,0-2,1 (12H, m, 3,4,5,7,9,11-CH_2); 3,1 (2H, pl s, 2-CH_2) un 9,1 m.d. (2H, pl s, NH_2^*).

3,3,5-Trimetil[2,2,6,6-$^2H_4$] cikloheksanons (**d_4-2f**)

Ketona **2f** (0,98 g; 7 mmol), K_2CO_3 (0,1 g; 0,7 mmol) un D_2O (2,1 ml) maisījumu vāra 20 h. Pēc atdzesēšanas reakcijas maisījumam pievieno ēteri (5 ml), atdala D_2O. Ēteri aiztvaicē, atlikumam pievieno D_2O (2,1 ml) un K_2CO_3 (0,1 g; 0,7 mmol) un vāra 20 h. Atdzesē, pievieno ēteri (5 ml), atdala D_2O. Ēteri aiztvaicē, atlikumam pievieno D_2O (2,1 ml) un K_2CO_3 (0,1 g; 0,7 mmol) un vāra 20 h. Pēc atdzesēšanas reakcijas produktu ekstrahē ar ēteri (2×10 ml). Ekstraktu nofiltrē caur 1 cm biezu silikagela slāni un šķīdinātāju aiztvaicē.

Iegūst **d_4-2f** (0,8 g; 82%) eļļas veidā; ^{1}H-KMR ($CDCl_3$, TMS) δ: 0,89 (3H, s, 3-CH_3); 1,00 (3H, d, J= 7 Hz, 5-CH_3); 1,04 (3H, s, 3-CH_3); 1,0-1,8 (2H, m, 4-CH_2); 1,89 (1H, m, 5-CH).

1-[$^2H_3$]Metil-3,3,5-trimetil[2,2,6,6-$^2H_4$]cikloheksanols (**d_7-3f**)

Pie 1M metilmagnija bromīda šķīduma ēterī (15 ml; 15 mmol), kas atdzesēts līdz 0° C piepilina ketona **d_4-2f** (0,72 g; 5 mmol) šķīdumu ēterī (10 ml). Pēc 0,5 h maisīšanas uzmanīgi piepilina pies. NH_4Cl ūdens šķīdumu (20 ml). Atdala organisko fāzi un ūdens fāzi ekstrahē ar ēteri (2×10 ml). Apvienotos ekstraktus mazgā ar pies. NaCl šķīdumu un žāvē virs $MgSO_4$. Pēc šķīdinātāja aiztvaicēšanas atlikumu attīra uz silikagela kolonas (50 cm^3), eluējot ar petrolētera-EtOAc (20:1, 10:1) maisījumu. Iegūst **d_7-3f** (0,68 g; 83%) ar k.t. 79-81°C; ^{1}H-KMR ($CDCl_3$, TMS) δ: 0,62 (1H, d, J= 13 Hz); 0,89 (3H, s, 3-CH_3); 0,90 (3H, d, J= 7 Hz, 5-CH_3); 0,96 (1H, s, OH); 1,09 (3H, s, 3-CH_3); 1,40 (1H, dd, J= 13 Hz un 3 Hz) un 1,87 m.d. (1H, m, 5-CH).

1-[$^2H_3$]Metil-3,3,5-trimetil[2,2,6,6-$^2H_4$]cikloheksān[^{2}H]ols (**d_8-3f**)

Cikloheksanola **d_7-3f** (0,1 g; 6 mmol) šķīdumam ēterī (2 ml) pievieno D_2O (1 ml). Pēc 24 h maisīšanas atdala D_2O fāzi un reakcijas maisījumam pievieno svaigu D_2O (1 ml). Pēc 24 h maisīšanas atdala ētera fāzi un D_2O fāzi ekstrahē ar ēteri (2×10 ml). Ekstraktu nofiltrē caur 1 cm biezu $MgSO_4$ slāni un šķīdinātāju aiztvaicē. Iegūst **d_8-3f** (75 mg, 75%) ar k.t. 78-80°C; ^{1}H-KMR ($CDCl_3$, TMS) δ: 0,62 (1H, d, J= 13 Hz); 0,89 (3H, s, 3-CH_3);

0.90 (3H, d, J= 7 Hz, 5-CH_3); 1,09 (3H, s, 3-CH_3); 1,40 (1H, dd, J= 13 Hz un 3 Hz) un 1,87 m.d. (1H, m, 5-CH).

Cikloalkanolu **3a**-*ax*, **40**-*ax,eq*, **3f**-*ax*, d_8-**3f**-*ax*; **48** Ritera reakcija. Amīdu **49-52**-*ax.eq* un d_8-**51**-*ax,eq* iegūšanas vispārīgā metode.

Pie cikloalkanola (2 mmol), trimetilsililcianīda (0,54 ml; 4 mmol) un etiķskābes (0,32 ml) maisījuma, kas atdzesēts līdz $0^{\circ}C$, piepilina sērskābi (0,32 ml; 6 mmol). Sērskābi pievieno ~5 min laikā, uzturot reakcijas maisījuma temperatūru zem $+5^{0}$ C. Pēc 23 h reakcijas maisījumu izlej ledus ūdenī (20 ml) un neitralizē ar 20% NaOH ūdens šķīdumu. Reakcijas produktu no ūdens fāzes ekstrahē ar ēteri (3×20 ml). Apvienotos ekstraktus mazgā ar pies. NaCl šķīdumu, žāvē virs $MgSO_4$ un šķīdinātāju aiztvaicē.

N-Formil-1,*t*- un *c*-3-dimetilcikloheksān-*r*-1-amīni (**49**-*ax*) un (**49**-*eq*)

Cikloheksanola **3a**-*ax* reakcijas produktu attīra uz silikagela kolonas (50 cm^3), eluējot ar petrolētera-EtOAc maisījumu (4:1, 3:1, 2:1). Iegūst **49**-*ax* un **49**-*eq* maisījumu (0,25 g; 80%)

Tīri izomēro amīdu **49**-*ax* un **49**-*eq* paraugi iegūti pēc sekojošas metodes:
pie ētera (1,5 ml) un 10% NaOH (1,5 ml) maisījuma pievieno amīna hidrogenhlorīdu **5a**-*ax* vai **5a**-*eq* (16 mg; 0,1 mmol). Pēc 2 h maisīšanas, atdala ētera fāzi un pievieno pie skudrskābes (0,41 ml) un etiķskābes anhidrīda (0,81 ml) maisījuma. Pēc 14 h reakcijas maisījumu ietvaicē un atlikumu attīra uz silikagela kolonas (10 cm^3), eluējot ar petrolētera-EtOAc maisījumu (2:1, 1:1).

Iegūst **49**-*ax* (10 mg, 65%), eļļas veidā; ^{1}H-KMR ($CDCl_3$, TMS) δ: 0,88 (3H, d, J= 6,5 Hz, 3-CH_3); 1,33 un 1,40 (kopā 3H, abi s, 1-CH_3); 0,8-2,3 (9H, m, cikla protoni); 5,1 un 5,6 (kopā 1H, abi pl s, NH); 8,11 un 8,24 m.d. (kopā 1H, abi d, J= 2 Hz un 12,5 Hz, CHO);

49-*eq* (9 mg, 58%) eļļas veidā; ^{1}H-KMR ($CDCl_3$, TMS) δ: 0,89 un 0,91 (kopā 3H, abi d, J= 6,5 Hz, 3-CH_3); 1,34 un 1,42 (kopā 3H, abi s, 1-CH_3); 1,1-2,1 (9H, m, cikla protoni); 5,2 un 5,9 (kopā 1H, abi pl s, NH); 8,03 un 8,32 m.d. (kopā 1H, abi d, J= 2 Hz un 12,5 Hz, CHO).

N-Formil-*t*- un *c*- 4-*terc*-butil-1-metilcikloheksān-*r*-1-amīni (**50**-*ax*) un (**50**-*eq*)

No cikloheksanola **40**-*ax* iegūst amīdu **50**-*ax* un **50**-*eq* maisījumu (0,37 g; 94 %); no cikloheksanola **40**-*eq* iegūst amīdu **50**-*ax* un **50**-*eq* maisījumu (0,37 g; 94 %); Abu reakciju produktus apvieno un sadala uz silikagela kolonas (50 cm^3), eluējot ar petrolētera-EtOAc maisījumu (1:1).

Iegūst **50**-*ax* (0,62 g) ar k.t. 91-92°C; ^{1}H-KMR ($CDCl_3$, TMS) δ: 0.85 (9H, s, *terc*-Bu); 1,33 un 1,39 (kopā 3H, abi s, 1-CH_3); 0,6-2,3 (9H, m, cikla protoni); 5,0 un 5,6 (kopā 1H, abi pl s, NH); 8,14 un 8,21 m.d. (kopā 1H, abi d, J= 2 Hz un 12,5 Hz, CHO);

50-*eq* (48 mg) ar k.t. 101-102°C; ^{1}H-KMR ($CDCl_3$, TMS) δ: 0,86 un 0,87 (kopā 9H, abi s, *terc*-Bu); 1,32 un 1,39 (kopā 3H, abi s, 1-CH_3); 0,6-2,2 (9H, m, cikla protoni); 5,2 un 5,8 (kopā 1H, abi pl s, NH); 8,04 un 8.32 m.d. (kopā 1H, abi d, J= 1,5 Hz un 12,5 Hz. CHO).

N-Formil-1,3,3, *t*- un *c*- 5-tetrametilcikloheksān-*r*-1-amīni (**51**-*ax*) un (**51**-*eq*)

Cikloheksanola **3f**-*ax* reakcijas produktus sadala uz silikagela kolonas (50 cm^3), eluējot ar petrolētera-EtOAc maisījumu (4:1, 3:1, 2:1).

Iegūst **51**-*ax* (0,27 g; 74%) ar k.t. 82-83° C; ^{1}H-KMR ($CDCl_3$, TMS) 0,8-1,0 (9H. m, 3,3,5-CH_3); 1,30 un 1,38 (kopā 3H, abi s, 1-CH_3); 0,7-2,2 (7H, m, cikla protoni); 5,3 un 5,7 (kopā 1H, abi pl s, NH); 8,06 un 8,24 m.d. (kopā 1H, abi d, J= 2 Hz un 12,5 Hz, CHO);

51-*eq* (20 mg; 6%) ar k.t. 101-102° C; ^{1}H-KMR ($CDCl_3$, TMS) 0,8-1,1 (9H, m, 3,3,5-CH_3); 1,44 un 1,51 (kopā 3H, abi s, 1-CH_3); 0,7-2,2 (7H, m, cikla protoni); 5,3 un 6,0 (kopā 1H, abi pl s, NH); 7,99 un 8,29 m.d. (kopā 1H, abi d, J= 2 Hz un 12,5 Hz, CHO).

N-[^{2}H]Formil-1-[$^2H_3$]metil-3,3, *t*- un *c*- 5-trimetil[2,2,6,6-$^2H_4$]cikloheksān-*r*-1-amīni (**d_8-51**-*ax*) un (**d_8-51**-*eq*)

No cikloheksanola **d_8-3f**-*ax* iegūst amīdu **d_8-51**-*ax* un **d_8-51**-*eq* (0,27 g; 70%) maisījumu. ^{1}H-KMR ($CDCl_3$, TMS) 0,8-1,1 (9H, m, 3,3,5-CH_3); 0,6-1,9 (3H, m, cikla protoni); 5,2 un 5,7 m.d. (kopā 1H, abi pl s, NH).

N-Formil-2,4,4-trimetiladamantān-2-amīni (**52**-*ax*) un (**52**-*eq*)

Adamantanola **48** reakcijas produktus sadala uz silikagela kolonas (120 cm^3), eluējot ar petrolētera-EtOAc maisījumu (2:1).

Iegūst **52**-*ax* (253 mg; 57%) ar k.t. 128-130° C; ^{1}H-KMR ($CDCl_3$, TMS) δ: 1,11, 1,18, 1,26 (kopā 6H, visi s, 4,4-CH_3); 1,53 un 1,61 (kopā 3H, abi s, 1-CH_3); 1,0-2,4 (12H, m, cikla protoni); 5,3 un 5,7 (kopā 1H, abi pl s, NH); 8,05 un 8,24 m.d. (kopā 1H, abi d, J= 2,5 Hz un 12,5 Hz, CHO).

52-*eq* (70 mg; 16%) eļļas veidā. ^{1}H-KMR ($CDCl_3$, TMS) δ: 1,14 un 1,16 (kopā 6H, abi s, 4,4-CH_3); 1,62 un 1,67 (kopā 3H, abi s, 1-CH_3); 1,0-2,3 (12H, m, cikla protoni); 5,4 un 5,9 (kopā 1H, abi pl s, NH); 8,09 un 8,23 m.d. (kopā 1H, abi d, J= 2,5 Hz un 12,5 Hz, CHO).

t- *un c*-4-*terc*-Butil-1-metilcikloheksān-*r*-1-izonitrili (**53**-*ax*) un (**53**-*eq*)

Amīdu **50**-*ax* vai **50**-*eq* (0,3 g; 1,5 mmol) šķīdumu CH_2Cl_2 (95 ml) atdzesē līdz –70° C un pievieno diizopropiletilamīnu (1,62 ml; 10 mmol) un trifluoretiķskābes anhidrīdu (0,40 ml; 2,4 mmol). Maisa 10 min pie –70° C, pievieno pies. $NaHCO_3$ ūdens šķīdumu (30 ml) un atsilda līdz istabas temperatūrai. Atdala organisko fāzi, to mazgā ar pies. $NaHCO_3$ ūdens šķīdumu (30 ml) un žāvē virs $MgSO_4$. Šķīdinātāju aiztvaicē un atlikumu attīra uz silikagela kolonas (50 cm^3), eluējot ar petrolētera-EtOAc maisījumu (20:1).

Iegūst **52**-*ax* (0,13 g; 48%) ar k.t. 46-47°C; ^{1}H-KMR ($CDCl_3$, TMS) δ: 0,88 (9H, s, *terc*-Bu); 1,40 (3H, s, 1-CH_3) un 0,6-2,0 m.d. (9H, m, cikla protoni); IS ($CHCl_3$) ν_{max}= 2120 cm^{-1} (NC);

52-*eq* (0,21 g; 76%) ar k.t. 39-41°C; ^{1}H-KMR ($CDCl_3$, TMS) δ: 0,86 (9H, s, *terc*-Bu); 1,41 (3H, s, 1-CH_3) un 0,6-2,2 m.d. (9H, m, cikla protoni); IS ($CHCl_3$) ν_{max}= 2130 cm^{-1} (NC).

Izonitrilu (**53**-*ax*) un (**53**-*eq*) protonēšana Ritera reakcijas apstākļos

Pie izonitrila **50**-*ax* vai **50**-*eq* (30 mg; 0.17 mmol) pievieno līdz 0° C atdzesētu maisījumu (1ml), kuru pagatavo no sērskābes (2,5 ml), trimetilsililcianīda (4 ml) un etiķskābes (2,5 ml) un maisa istabas temperatūrā. Pēc 1 min, 10 min, 1 h, 5 h, 23 h un 31 h no reakcijas maisījuma noņem paraugus (0,05 ml) gāzu hromatogrāfiskajai analīzei. Pirms analīzes paraugu atšķaida ar ūdeni, pievieno 20% NaOH līdz bāziskai videi un

reakcijas produktus ekstrahē ar ēteri (0,5 ml). Reakcijā iegūto amīdu **50**-*ax* vai **50**-*eq* attiecība dota 8. tabulā (5. nodaļa).

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Eur. J. Med. Chem. 35 (2000) 1–11

S0223523400001537/FLA

Original article

Synthesis and structure–affinity relationships of 1,3,5-alkylsubstituted cyclohexylamines binding at NMDA receptor PCP site

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Received 15 March 1999; revised 14 December 1999; accepted 17 December 1999

Abstract – A series of 1,3,5-alkylsubstituted cyclohexylamines **2** were synthesized as ligands for the N-methyl-D-aspartate (NMDA) receptor phencyclidine (PCP) binding site. Pure diastereomers with defined configuration of amino group 2-*ax* and 2-*eq* were obtained. The optimal size of 1,3,5-substituents was determined for cyclohexylamines **2** with an equatorial amino group in the lowest energy conformation using Hansch analysis. According to the data, the lipophilic part of cyclohexylamines **2** does not discriminate between hydrophobic regions of the PCP binding site but rather recognizes this site as a whole lipophilic pocket. © 2000 Éditions scientifiques et médicales Elsevier SAS

NMDA receptor / PCP / cyclohexylamines / Hansch analysis

1. Introduction

The antagonism of the NMDA receptor has a potential for a wide range for therapeutic applications in the case of CNS disorders associated with pathological glutamate release from presynaptic neurones [1]. Non-competitive NMDA receptor antagonists are known to bind at a phencyclidine (PCP *figure 1*) binding site located inside the NMDA receptor cation channel [1, 2]. A number of structurally diverse compounds have been shown to act at the PCP binding site including structural analogues of PCP, dizocilpine (MK-801) (*figure 1*), ketamine, dextromethorphan, etc. [3]. However, it has been recognized that the high affinity NMDA receptor ion channel blockers have undesirable psychotomimetic side effects while moderate affinity agents are clinically tolerated [1, 3]. It has been shown that 1-amino-3,5-substituted adamantane derivatives **1** (*figure 1*) exhibit a moderate affinity for the NMDA receptor [4]. Moreover, two representatives of this class, i.e. 1-aminoadamantane (amantadine) and 1-amino-3,5-dimethyladamantane (memantine) are already used clinically for the treatment of Parkinson's disease and dementia [1].

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However, the number of 1-aminoadamantanes possessing a considerable affinity for the NMDA receptor is limited, therefore only scant information on the structure–affinity relationships is available for such compounds [3]. This prompted us to design and synthesize 1-aminoadamantane **1** structural analogues 1,3,5-substituted cyclohexylamines **2** (*figure 1*). Systematic variation of the substituents from hydrogen to propyl groups would allow the estimation of the dependence of the size of lipophilic globule on the binding affinity.

2. Chemistry

The synthesis of 1,3,5-alkylcyclohexylamines **2** (*figure 2*) was performed starting with 2-cyclohexen-1-ones **3a–g** summarized in *table I*. Compounds **3a–d** are commercially available. The rest of the 2-cyclohexen-1-ones **3e–g** were prepared according to the literature procedure [5] as shown in *figure 3*.

2-Cyclohexen-1-ones **3** were then converted to cyclohexanones **4a–d** and **f–m** (*table II*) by 1,4-conjugate addition of organocuprates prepared in situ from alkylmagnesium halides and copper (I) chloride. In the case of enone **3c** the addition of diethyl- and dipropylmagne-

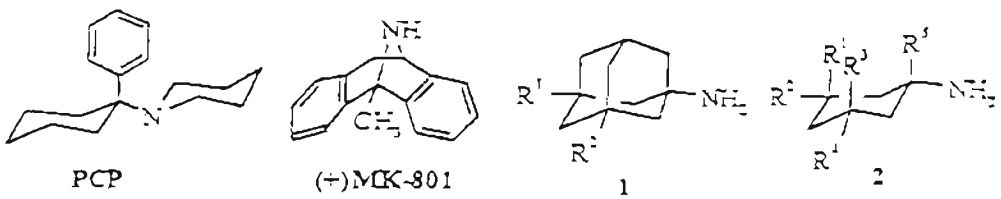

Figure 1. Chemical structure of PCP, MK-801, 3,5-substituted amino adamantanes **1** and 1,3,5-substituted cyclohexylamines **2**.

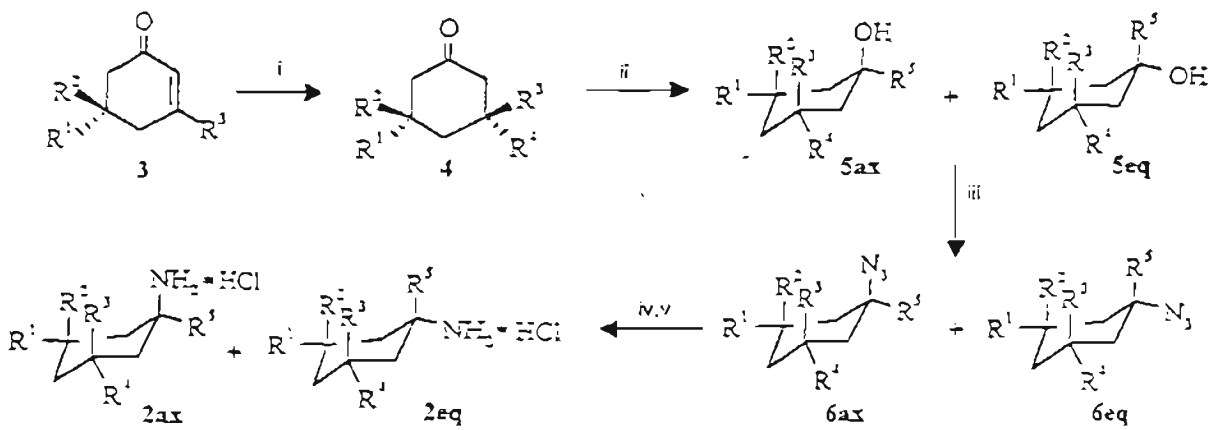

Figure 2. The general scheme for the synthesis of 1,3,5-substituted cyclohexylamines **2**. Conditions: i) R^4_2CuMgX; ii) R^5MgX; iii) A: HN_3, $TiCl_4$ B: $TMSN_3$, $BF_3{\cdot}Et_2O$; iv) $LiAlH_4$; v) HCl.

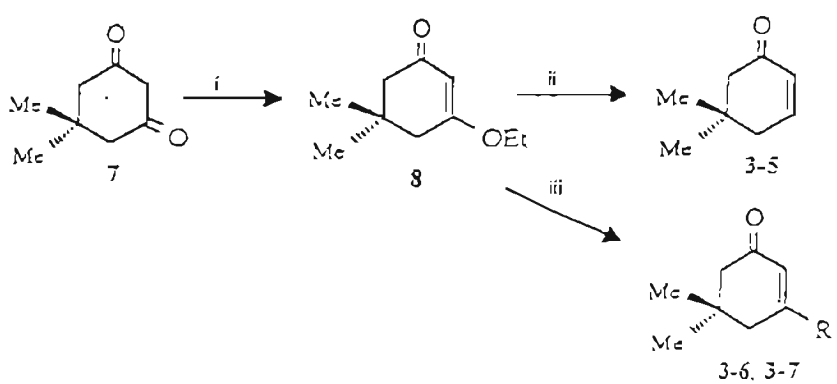

Figure 3. The preparation of cyclohexen-2-ones **3**. Conditions: i) EtOH, TsOH; ii) $LiAlH_4$ then 10% H_2SO_4; iii) RMgI then 5% H_2SO_4.

Table I. Alkylsubstituted 2-cyclohexen-1-ones 3.

Compound	R^1	R^2	R^3	Yield[a] (%)
3a	H	H	H	–
3b	H	H	Me	–
3c	H	Me	Me	–
3d	Me	Me	Me	–
3e	Me	Me	H	70
3f	Me	Me	Et	40
3g	Me	Me	Pr	40

[a] commercially available if omitted.

Table II. Alkylsubstituted cyclohexanones 4.

Compound	R^1	R^2	R^3	R^4	Yield[a] (%)
4a	H	H	H	Me	–
4b	H	H	H	Et	63
4c	H	H	H	Pr	79
4d	H	H	Me	Me	78
4e	Me	H	H(Me)	Me(H)	86[b]
4f	Me	H	Me	Me	57
4g	Me	H	Et	Me	78
4h	Me	H	Pr	Me	82
4i	Me	Me	H	Et	54
4j	Me	Me	H	Pr	74
4k	Me	Me	Me	Me	–
4l	Me	Me	Et	Et	84
4m	Me	Me	Pr	Pr	79

[a] commercially available if omitted. [b] prepared by oxidation of 3,5-dimethylcyclohexanol (*figure 5*).

Table III. Alkylsubstituted cyclohexanols 5.

Compound	R^1	R^2	R^3	R^4	R^5	Yield[a] (%)
5a-*ax*, 5a-*eq*	H	H	H	Me	Me	88
5b-*ax*, 5b-*eq*	H	H	H	Et	Me	93
5c-*ax*, 5c-*eq*	H	H	H	Pr	Me	93
5d	H	H	Me	Me	Me	78
5e-*eq*	Me	H	H	Me	Me	15
5f-*ax*	Me	H	Me	Me	Me	85
5g-*ax*	Me	H	Et	Me	Me	94
5h-*ax*	Me	H	Pr	Me	Me	88
5i-*ax*	Me	Me	H	Et	Me	84
5j-*ax*	Me	Me	H	Pr	Me	88
5k	Me	Me	Me	Me	Me	93
5l	Me	Me	Me	Me	Et	92
5m	Me	Me	Me	Me	Pr	85
5n	Me	Me	Et	Et	Me	87
5o	Me	Me	Pr	Pr	Me	90
5p	H	H	H	H	Me	–

[a] commercially available if omitted.

siumcuprates yielded mainly isomers **4g** and **4h** (> 95%, GC) with 3- and 5-methyl groups in *cis* configuration as a result of preferred anti-parallel addition to 5-substituted cyclohexenones [6]. This was confirmed by analysis of the ^{1}H-NMR spectra of final amines **2g** and **h** (see below).

Ketones **4** were treated with alkylmagnesium halides providing cyclohexanols **5a–m** (*table III*). Noteworthy, 3-monosubstituted cyclohexanones **4a–c** afforded the mixtures of both isomers **5a–c**-*ax* and **5a–c**-*eq*, whereas 3,3,5-trisubstituted cyclohexanones **4f–j** gave cyclohexanols **5f–j**-*ax* as the sole product (-*ax* and -*eq* indicates the axial or equatorial position of heteroatom functionality in the most favourable conformation of diastereomer (*figure 4*)). Such a stereochemical outcome was in agreement with the published examples of nucleophilic additions to 3-methyl- and 3,3,5-tetramethylcyclohexanones [7]. The isomeric mixtures of alcohols **5a–c** were used for the next step, as either isomer yields the same ratio of products [8]. Samples of pure isomers **5a–c**-*ax* and **5a–c**-*eq* were obtained by flash chromatography for characterization purposes only.

1, *cis*-3, *cis*-5-Trimethylcyclohexanol **5e**-*eq* was prepared by a different route (*figure 5*). Thus, oxidation of a commercially available isomeric mixture of 3,5-dimethylcyclohexanol **9** resulted in a mixture of *cis*- and *trans*-dimethylcyclohexanones **4e**, separation of which has been described [9]. However, we found it more convenient to separate trimethylcyclohexanol with the desired *cis* geometry of 3,5-methyl groups **5e**-*eq* from a mixture of isomeric alcohols by flash chromatography after the Grignard reaction of ketones **4e**.

The azidation of cyclohexanols **5a–n** in the presence of a Lewis acid turned out to be the method of choice to introduce the amino functionality. The conversion to azides **6a–p** (*table IV*) was performed either by using hydrazoic acid and titanium tetrachloride (method A) [8] or by applying trimethylsilyl azide as a hydrazoic acid equivalent in combination with boron trifluoride etherate (method B) [10]. The latter method avoids the use of poisonous and explosive hydrazoic acid. Isomeric azides **6a–c**-*ax*,-*eq* and **6e–j**-*ax*, -*eq* were successfully separated by flash chromatography on silica gel. The reduction of azides **6a–p** to the corresponding cyclohexylamines **2a–p** (*table V*) provided pure diastereomers **2a–c** and **e–j**-*ax* and **2a–c** and **e–j**-*eq*. The conformational analysis of cyclohexylamine salts **2a–p** (*figure 4*) was made by a semiquantitative assessment of conformational energies using A and U values [11]. For amine isomers **2a–c**-*ax*, **2e**-*ax* and **2f–j**-*ax* the conformation with the amino group in the axial position was found to be energetically favoured by 3.4 kcal/mol, 8.8 kcal/mol and 5.1 kcal/mol,

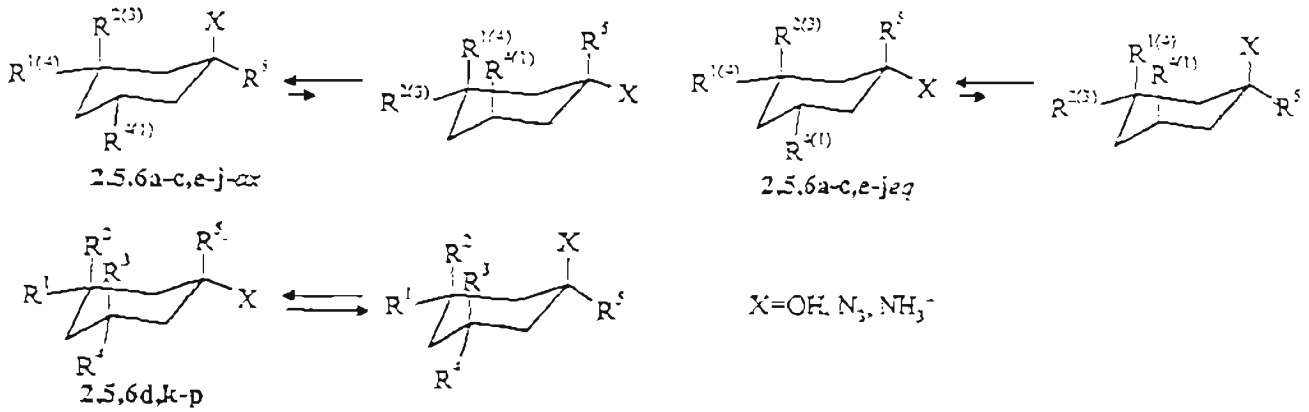

Figure 4. Conformational analysis of 1,3,5-substituted cyclohexanols 5, cyclohexylazides 6 and cyclohexylamines 2.

respectively. For diastereomers 2a–c-*eq*, 2e-*eq* and 2f–j-*eq* the conformation with the amino group in the equatorial position was found to be energetically favoured by 3.9 kcal/mol, 9.2 kcal/mol and 5.6 kcal/mol, respectively. Such an energy difference corresponds to more than 99% of the population of the favoured conformer. Thus, diastereomers 2a–c and 2e–j can be regarded as conformationally biased structures with a defined position of the amino group. In the case of symmetrical cyclohexylamines 2d and 2p the energy difference was only 0.2–0.3 kcal/mol in favour of the conformer with the equatorial amino group. This means that an *eq*-amino conformer is only slightly preferred. The same could also be true for amines 2k–o, however, the cut-off value of both chair conformers is exceeded in these cases. Therefore, a population of non-chair conformations could also be expected in those cases. This, however, can be estimated only on the basis of more extensive conformational studies.

The configuration of the amino group in diastereomers of 1,3-disubstituted cyclohexylamines 2a–c and 1,3,5-trimethylcyclohexylamine 2e could not be determined unequivocally by ^{1}H-NMR spectra due to the small difference of the chemical shifts. To solve this problem ^{13}C-NMR spectra of the diastereomers 2a-*ax* and 2a-*eq* were recorded. The signal assignment was made by correlation with already interpreted spectra of 1,3-dimethylcyclohexanols 5a-*ax* and 5a-*eq* [12]. As for cyclohexanols, the 1-methyl group in amine 2a-*eq* was shifted upfield by 5.8 ppm compared to that in its counterpart 2a-*ax* due to the shielding δ-effect. Noteworthy, amine 2a-*ax* had about 0.2 min shorter retention time than 2a-*eq* in GC analysis. This is a known property of conformationally biased cyclohexanols which stems from the smaller tendency of the axial substituent to form hydrogen bonds [13]. For cyclohexylamine 2a homologues 2b and 2c as well as for 2e, the isomers with shorter retention times were assigned to be 2b and c-*ax* and 2e-*ax*.

In the case of 1,3,3,5-tetrasubstituted cyclohexylamines 2e–j, ^{1}H-NMR was used to determine the configuration of substituents. Axial 3-Me group protons in compounds 2e, f, i and j-*ax* were shifted downfield for ~0.25 ppm compared to the corresponding isomers 2e, f, i and j-*eq*. Such an effect was attributed to the more pronounced σ-compression effect of the electronegative axial amino

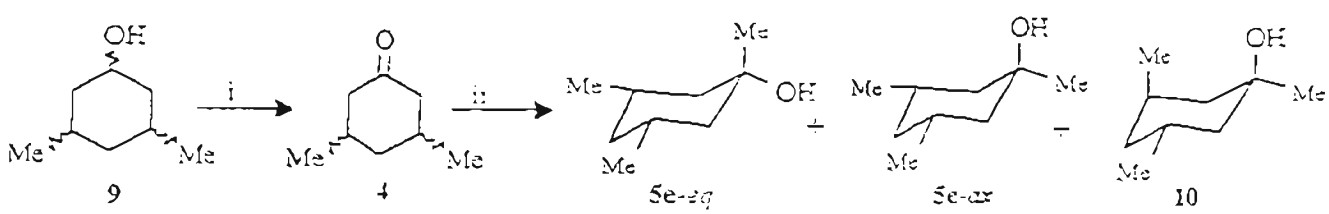

Figure 5. The synthesis of 1,3,5-trimethylcyclohexanol 5e-*eq*. Conditions: i) H_2SO_4, CrO_3; ii) MeMgX.

Table IV. Alkylsubstituted cyclohexyl azides 6.

Compound	R^1	R^2	R^3	R^4	R^5	Procedure	Yield (%)
6a-*ax*	H	H	H	Me	Me	B	24
6a-*eq*							12
6b-*ax*	H	H	H	Et	Me	A	26
6b-*eq*							4
6c-*ax*	H	H	H	Pr	Me	A	24
6c-*eq*							11
6d	H	H	Me	Me	Me	A	65
6e-*ax*	Me	H	H	Me	Me	B	43
6e-*eq*							19
6f-*ax*	Me	H	Me	Me	Me	A	42
6f-*eq*							12
6g-*ax*	Me	H	Et	Me	Me	A	47
6g-*eq*							12
6h-*ax*	Me	H	Pr	Me	Me	A	44
6h-*eq*							9
6i-*ax*	Me	Me	H	Et	Me	B	45
6i-*eq*							12
6j-*ax*	Me	Me	H	Pr	Me	A	54
6j-*eq*							7
6k	Me	Me	Me	Me	Me	A	67
6l	Me	Me	Me	Me	Et	A	39
6m	Me	Me	Me	Me	Pr	A	65
6n	Me	Me	Et	Et	Me	A	66
6o	Me	Me	Pr	Pr	Me	A	61
6p	H	H	H	H	Me	A	27

Table V. Alkylsubstituted cyclohexylamine hydrochlorides 2[a].

Compound	R^1	R^2	R^3	R^4	R^5	Yield (%)
2a-*ax*	H	H	H	Me	Me	63
2a-*eq*						48
2b-*ax*	H	H	H	Et	Me	66
2b-*eq*						43
2c-*ax*	H	H	H	Pr	Me	80
2c-*eq*						81
2d	H	H	Me	Me	Me	73
2e-*ax*	Me	H	H	Me	Me	74
2e-*eq*						55
2f-*ax*	Me	H	Me	Me	Me	74
2f-*eq*						57
2g-*ax*	Me	H	Et	Me	Me	68
2g-*eq*						60
2h-*ax*	Me	H	Pr	Me	Me	57
2h-*eq*						36
2i-*ax*	Me	Me	H	Et	Me	69
2i-*eq*						44
2j-*ax*	Me	Me	H	Pr	Me	83
2j-*eq*						44
2k	Me	Me	Me	Me	Me	82
2l	Me	Me	Me	Me	Et	74
2m	Me	Me	Me	Me	Pr	88
2n	Me	Me	Et	Et	Me	78
2o	Me	Me	Pr	Pr	Me	72
2p	H	H	H	H	Me	69

[a] R^a = H if omitted.

group of **2e, f, 2i** and **j-*ax*** compared to the axial 1-methyl group of isomers **2e, f, i** and **j-*eq*** (for similar effects in cyclohexanols see ref. [14, 15]). The σ-compression effect of the axial amino group was not observed for the 3-methyl groups of compounds **2g** and **h-*ax***. This confirmed *cis* configuration of 3- and 5-methyl groups (both equatorial) in cyclohexylamines **2g** and **h**. 1-Methyl group signals in amines **2e–j-*ax*** were shifted upfield by 0.03–0.16 ppm compared to the signals in isomers **2e–j-*eq***. This again could be explained by the deshielding σ-compression effect of the axial 3-substituent on the axial 1-methyl group in isomers **2e–j-*eq***. It is necessary to note that isomers **2e–j-*ax*** had shorter retention times compared to **2e–j-*eq*** in GC analysis with a difference of ~0.5 min.

3. Pharmacology

The NMDA receptor PCP binding site affinities of cyclohexylamines **2** were determined by radioligand ([^{3}H]MK-801) displacement studies on rat cortical membrane preparations and are listed in *table VI*. A full description of the affinity determination procedure and

Table VI. Ki, log(1/Ki), and log(P) values for alkylsubstituted cyclohexylamine hydrochlorides 2.

Compound	Ki (μM)	log (1/Ki)	log (P)	Compound	Ki (μM)
2a-*eq*	65.29	−1.82	2.43	2a-*ax*	52.6
2b-*eq*	49.10	−1.69	2.96	2b-*ax*	49.28
2c-*eq*	49.18	−1.69	3.49	2c-*ax*	70.95
2d	32.20	−1.57	2.97		
2e-*eq*	19.21	−1.28	2.92	2e-*ax*	30.0
2f-*eq*	4.66	−0.67	3.46	2f-*ax*	7.74
2g-*eq*	15.14	−1.18	3.99	2g-*ax*	13.32
2h-*eq*	57.76	−1.76	4.52	2h-*ax*	24.02
2i-*eq*	2.88	−0.46	3.99	2i-*ax*	5.18
2j-*eq*	13.40	−1.13	4.52	2j-*ax*	15.01
2k	1.47	−0.17	4.00		
2l	2.28	−0.36	4.53		
2m	8.09	−0.91	5.06		
2n	3.16	−0.50	5.06		
2o	16.48	−1.22	6.13		
2p	144.33	−2.16	1.94		

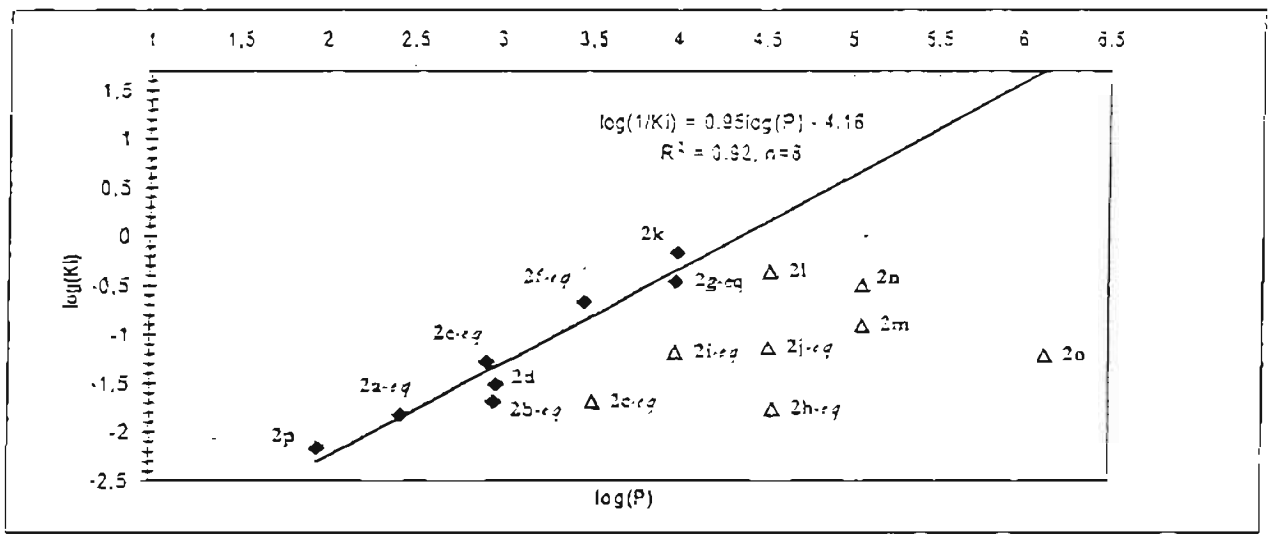

Figure 6. Hansch analysis of cyclohexylamines **2a–c**, **e–j-*eq*** and **2d**, **k–p**. Squares indicate the compounds for which the linear relationship log(1/K_i) = alog (P) + c takes place.

more extensive studies on the biological activity of cyclohexylamines 2 were reported separately [16].

4. Results and discussion

QSAR analysis has already been carried out for a number of the NMDA receptor PCP site ligands [3]. These studies revealed that this binding site is a size-restricted pocket and both aromatic and amino groups are necessary for the high affinity binding [3, 17]. The importance of hydrophobic effect in binding of ligands has also been reported [18].

In the pharmacophore model developed by molecular modelling, two hydrophobic regions were recognized [3]. One of them requires an aromatic ring for high affinity binding and corresponds to the phenyl ring of the PCP molecule or the aromatic ring of MK-801. The other, common lipophilic size restricted area, corresponds to the cyclohexyl ring of PCP or second aromatic ring of MK-801.

Cyclohexylamine 2 homologues differ in their lipophilicity and steric requirements. Hansch analysis [19] was therefore chosen for SAR evaluation of cyclohexyl amines with an equatorial amino group (in the lowest energy conformation) **2a–c** and **e–j-*eq*** and **2d** and **2k–p**, as they might be regarded as aminoadamantane **1** structural analogues. Equation (1) expresses affinity as a function of log P (describing a hydrophobic effect) and a steric descriptor S. The strength of reinforced ionic binding between the receptor active centre and protonated amino group was assumed to be equal for these compounds. Log P values (*table VI*) for this homologue series were calculated from fragmental constants [20] using software ACD/Log P 1.0.

$$\log (1/Ki) = a \log (P) + b \log (S) + c \quad (1)$$

Figure 6 shows that for cyclohexylamines **2a**, **b** and **e–g-*eq*** and **2d**, **k** and **p**, affinity expressed as log (1/Ki) is a linear function of lipophilicity (log P). This indicates that steric factor (S) is negligible in these cases, i.e. these compounds fit properly in the PCP binding site. In the case of more bulky compounds such as **2c** and **h–j-*eq*** and **2l–o**, the steric factor becomes more important resulting in an obvious decline from linearity. A nearly perfect linear relationship observed for cyclohexylamines **2d**, **k** and **p** along with **2a**, **b** and **e–g-*eq*** was somewhat surprising, because only slight preference for the conformation with an equatorial amino group was expected for them. The possible reason could be that a conformer with an axial amino group also binds with the receptor. Very similar affinities of conformationally biased cyclohexylamine isomers **2-*ax*** and **2-*eq*** implies that (*table VI*).

Cyclohexylamines **2a–c** and **e–j-*eq*** and **2d** and **k–p** were superimposed with one of the most potent PCP site ligands (+)-MK-801 (*figure 7a*). Notably, the amines **2a**, **b** and **e–g-*eq*** and **2d**, **k** and **p** showed a perfect fit in the receptor site (determined by Hansch analysis) and also a perfect fit into the cavity between aromatic rings of MK-801. Moreover, amines **2c** and **h–j-*eq*** and **2l–o** with

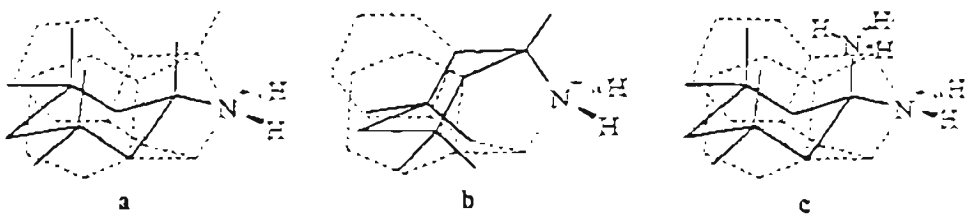

Figure 7. Schematic representation of superimposition of 1,3,5 substituted cyclohexylamines 2 with (+)MK-801 (dotted bonds).

the axial 1,3-substituents larger than methyl or equatorial 3,5-substituents larger than ethyl group markedly exceed MK-801 dimensions and, consequently display a relatively lower affinity for the NMDA receptor.

Aminoadamantanes **1** have been suggested to occupy the region corresponding to the cyclohexyl ring of PCP or one of the aromatic ring of MK-801 [3]. Their moderate affinity has been explained by their large steric bulk not sufficiently tolerated in this region. The present investigation based on more rich information about SAR gives evidence that aminocyclohexanes **2**, and hence aminoadamantanes **1** do not discriminate between hydrophobic regions of PCP binding site but rather recognize this site as a whole lipophilic pocket. The medium affinity of sterically tolerated cyclohexylamines **2** and aminoadamantanes **1** is obviously due to the lack of an aromatic system as a pharmacophore element necessary for high affinity binding.

The similar binding of cylohexylamines with an axial amino group 2-*ax* and diastereomers with an equatorial amino group 2-*eq* can be explained in several ways. The superimposition of aminocyclohexanes 2-*ax* with MK-801 taking the nitrogen atom as a common point also gave a good fit of the 3,5-substituted cyclohexyl globule with MK-801 (*figure 7b*). The lipophilic part of 2-*ax* markedly exceeds the MK-801 dimensions when axial substituents are larger than methyl and equatorial substituents are larger than ethyl, i.e. the steric requirements of 2-*ax* binding are similar to 2-*eq* (*figure 7a*).

It cannot be excluded that the axial amino group in 2-*ax* may bind to another ionic site point of the PCP binding site. When cyclohexylamine 2-*ax* is superimposed with MK-801 the same way as 2-*eq*, the axial amino group of 2-*ax* is situated next to MK-801 5-methyl substituent (*figure 7c*). Recent SAR studies have revealed that additional site point might be located in the proximity of MK-801 5-methyl group [18].

In summary, we have developed a new class of the medium affinity NMDA receptor ion channel blockers based on a cyclohexylamine structure and established their structure–affinity relationships which could promote a rational design of the new PCP binding site ligands.

5. Experimental protocols

5.1. Chemistry

Melting points were determined on a Gallenkamp apparatus and are uncorrected. Microanalyses were performed on a Karlo Erba Instruments EA1108 and the results where within ± 0.4% of the calculated values. NMR spectra were recorded on a Brucker WH 90 and Brucker WM 360 spectrometers. Column chromatography was performed on Kieselgel 63–100 μm. TLC analyses were performed on Kieselgel 60 F_{254} plates (Merck). Eluent: hexane/ethyl acetate, visualization agent: iodine vapours. Purity of the final products were determined by GC analysis (MN-OV-1 (Fused Silica), 25 m × 0.53 mm, d_f = 1.0 μ, 50–270 °C (10° C/min)) and were found to be more than 99%.

5.1.1. Cyclohexenones 3

5.1.1.1. 3,3-Dimethyl-5-propyl-2-cyclohexen-1-one 3g

A solution of 3-ethoxy-5,5-dimethyl-2-cyclohexen-1-one **8** [21] (5.04 g, 30 mmol) in ether was added dropwise to a stirred solution of propylmagnesium iodide prepared from 90 mg of magnesium and 90 mmol of 1-iodopropane in 60 mL of ether. After being stirred for 1 h at ambient temperature the reaction mixture was treated with 5% H_2SO_4 solution. The organic phase was separated, washed with brine, dried over $MgSO_4$ and evaporated to give a crude oil which was separated on a silica gel column, eluting with a hexane/ethyl acetate mixture. Cyclohexenone (3g) was obtained as a colourless oil (2.0 g, 70%). ^{1}H-NMR ($CDCl_3$, TMS) δ: 0.92 (3H, t, J = 7 Hz); 1.03 (6H, s); 1.3–1.75 (2H, m); 2.16 (2H, t, J = 7 Hz); 2.17 (2H, d, J = 1.5 Hz); 2.21 (2H, s) and 5.87 ppm (1H, t, J = 1.5 Hz).

Table VII. ^{1}H-NMR spectra of cyclohexanones 4.

Compound	^{1}H-NMR ($CDCl_3$, TMS) δ, ppm
4g	0.79 (3H, t, 7 Hz); 0.96 (3H, s); 1.06 (3H, d, 7 Hz), 1.22 (2H, m); 1.5–2.4 (5H, m)
4h	0.86 (3H, t, 6 Hz); 0.98 (3H, s); 1.01 (3H, d, 5 Hz), 1.05–1.35 (4H, m);1.55–2.05 (4H, m); 2.11 (2H, s); 2.34 (1H, m)
4i	0.88 (3H, s); 0.90 (3H, t, 7 Hz); 1.06 (3H, s); 1.15–1.45 (2H, m); 2.13 (2H, s); 1.45–2.45 (5H, m)
4j	0.87 (6H, m); 1.15 (3H, s); 1.15–1.45 (4H, m); 2.13 (2H, s); 1.45–2.45 (5H, m)
4l	0.78 (6H, t, 7 Hz); 1.04 (6H, s); 1.37 (2H, q, 7 Hz); 1.52 (2H, s); 2.16 (4H, s)
4m	0.87 (6H, m); 1.03 (6H, s); 1.25 (8H, m); 1.53 (2H, s); 2.16 (4H, s)

Cyclohexenones 3a–3d were purchased form Aldrich. Cyclohexenones 3e and 3f were prepared as described [5, 22].

5.1.2. General procedure for cyclohexanones 4

Anhydrous copper (I) chloride (7.5 mmol) was added to a cooled solution of alkylmagnesium iodide (15–18 mmol) in ether. The mixture was stirred in an inert atmosphere for 5 min and a solution of 2-cyclohexene-1-one 3 (10 mmol) in ether was added dropwise keeping the temperature below –5 °C. After the addition of ketone was completed, the reaction mixture was stirred for 1 h and carefully neutralised with saturated aqueous NH_4Cl solution. Traditional workup for Grignard reactions gave crude material that was separated on a silica gel column, eluting with a petroleum ether/ethyl acetate mixture. The cyclohexanones 4 were obtained as oils. The yields are listed in *table II*. The ^{1}H-NMR spectral data for all new cyclohexanones 4g–4j, l and m are given in *table VII*.

3-Methylcyclohexanone 4a and 3,3,5,5-tetramethylcyclohexanone 4k were available from Aldrich. Known cyclohexanones were prepared according to the general procedure: 3-ethyl- and 3-propylcyclohexanones 4b and 4c [23, 24]; 3,3-dimethyl-,3,5-dimethyl- and 3,3,5-trimethylcyclohexanones 4d–4f [25–27].

5.1.3. General procedure for cyclohexanols 5

An etheral solution of alkylmagnesium iodide (3–4 equivalents) was added dropwise to a cooled solution of cyclohexanone 2 in ether. The mixture was stirred for 1 h at ambient temperature and carefully destroyed with saturated aqueous ammonium chloride. Traditional workup for Grignard reactions followed by chromatography on a silica gel column eluting with petroleum ether/ethyl acetate provided cyclohexanols 5. The yields are listed in *table III*. The ^{1}H-NMR spectral data for all new cyclohexanols 5b, 5c, 5g–5i, 5n and 5o are given in *table VIII*.

Methylcyclohexanol 5p was purchased from Aldrich. Known cyclohexanols were prepared according to the general procedure: 1,3-dimethylcyclohexanols 5a [12]; 1,3,3-trimethyl- and 1,3,5- trimethylcyclohexanols 5d and 5e-*ex* [28, 29]; 1,3,3,5-tetramethyl- and 1,3,3,5,5-pentamethylcyclohexanols 5f-*ax*, 5k [15].

5.1.4. General procedures for cyclohexyl azides 6

Procedure A:

The alcohol 5 was mixed with 1.7–2 N hydrazoic acid (10–13 equivalents) solution in chloroform, and cooled in an ice bath. A solution of $TiCl_4$ (1.2 equivalents) in chloroform was added dropwise while the temperature was maintained below 5 °C. The mixture was stirred at room temperature for 24 h and passed down a column of

Table VIII. ^{1}H-NMR spectra of cyclohexanols 5.

Compound	^{1}H-NMR ($CDCl_3$, TMS) δ, ppm
5b-*ax*	0.84 (3H, t, 7 Hz); 1.17 (3H, s); 1.0–1.85 (12H, m)
5b-*eq*	0.87 (3H, t, 7 Hz); 1.21 (3H, s); 1.0–1.85 (12H, m)
5c-*ax*	0.86 (3H, t, 7 Hz); 1.18 (3H, s); 1.0–1.9 (14H, m)
5c-*eq*	0.86 (3H, t, 7 Hz); 1.19 (3H, s); 1.0–1.85 (14H, m)
5g-*ax*	0.80 (3H, s); 0.81 (3H, t, 7 Hz); 0.86 (3H, d, 6.5 Hz); 1.17 (3H, s); 0.9–2.0 (10H, m)
5h-*ax*	0.81 (6H, m); 0.86 (3H, d, 6.5 Hz); 1.17 (3H, s); 0.9–2.0 (12H, m)
5i-*ax*	0.87 (6H, m); 1.08 (3H, s); 1.18 (3H, s); 0.95–1.95 (10H, m)
5j-*ax*	0.88 (6H, m); 1.09 (3H, s); 1.18 (3H, s); 0.9–1.95 (12H, m)
5m	0.89 (9H, m); 1.21 (6H, s); 0.95–1.7 (11H, m)
5n	0.78 (6H, t, 7 Hz); 0.89 (3H, s); 1.19 (6H, s); 0.95–1.3 (7H, m); 1.3–2.05 (4H, m)
5o	0.86 (6H, t, 6.5 Hz); 0.88 (3H, s); 1.18 (6H, s); 0.9–1.3 (11H, m); 1.3–2.05 (4H, m)

Table IX. ^{1}H-NMR spectra of cyclohexyl azides 6.

Compound	^{1}H-NMR ($CDCl_3$, TMS) δ, ppm
6a-*ax*	0.89 (3H, d, 6.5 Hz); 1.31 (3H, s); 0.95–2.0 (9H, m)
6a-*eq*	0.92 (3H, d, 6.5 Hz); 1.28 (3H, s); 1.0–2.0 (9H, m)
6b-*ax*	0.88 (3H, t, 7 Hz); 1.29 (3H, s); 0.95–2.0 (11H, m)
6b-*eq*	0.88 (3H, t, 6.5 Hz); 1.27 (3H, s); 1.0–2.0 (11H, m)
6c-*ax*	0.88 (3H, t, 6.5 Hz); 1.29 (3H, s); 1.0–2.0 (13H, m)
6c-*eq*	0.88 (3H, t, 6.5 Hz); 1.27 (3H, s); 1.0–2.0 (13H, m)
6d	0.90 (3H, s); 1.08 (3H, s); 1.27 (3H, s); 1.0–1.95 (8H, m)
6e-*ax*	0.87 (6H, d, 6 Hz); 1.29 (3H, s); 0.90–2.1 (8H, m)
6e-*eq*	0.90 (6H, d, 6 Hz); 1.27 (3H, s); 1.0–1.9 (8H, m)
6f-*ax*	0.86 (3H, d, 6 Hz); 0.89 (3H, s); 1.09 (3H, s); 1.27 (3H, s); 0.95–1.9 (7H, m)
6f-*eq*	0.92 (3H, d, 6 Hz); 0.94 (3H, s); 0.97 (3H, s); 1.36 (3H, s); 0.95–2.0 (7H, m)
6g-*ax*	0.81 (6H, s and m); 0.86 (3H, d, 6 Hz); 1.27 (3H, s); 0.95–1.95 (9H, m)
6g-*eq*	0.81 (3H, t, 7 Hz); 0.87 (3H, s); 0.91 (3H, d, 6 Hz); 1.34 (3H, s); 0.95–?.?? (9H, m)
6h-*ax*	0.81 (3H, s); 0.84 (3H, d, 6 Hz); 0.87 (3H, m); 1.27 (3H, s); 1.0–2.0 (11H, m)
6h-*eq*	0.88 (6H, s and m); 0.91 (3H, d, 6 Hz); 1.34 (3H, s); 1.0–1.95 (11H, m)
6i-*ax*	0.91 (3H, t, 7 Hz); 0.92 (3H, s); 1.12 (3H, s); 1.31 (3H, s); 1.0–1.9 (9H, m)
6i-*eq*	0.92 (3H, t, 7 Hz); 0.97 and 0.99 (total 6H, s); 1.37 (3H, s); 1.0–1.9 (9H, m)
6j-*ax*	0.90 (6H, s and m); 1.10 (3H, s); 1.28 (3H, s); 0.95–1.9 (11H, m)
6j-*eq*	0.89 (3H, t, 7 Hz); 0.95 (3H, s); 0.98 (3H, s); 1.37 (3H, s); 1.0–1.9 (11H, m)
6k	0.89 (6H, s); 1.18 (6H, s); 1.29 (3H, s); 0.95–1.9 (6H, m)
6l	0.89 (6H, s); 0.96 (3H, t, 7 Hz); 1.19 (6H, s); 1.0–1.9 (8H, m)
6m	0.89 (6H, s); 0.93 (3H, m); 1.18 (6H, s); 1.0–1.8 (10H, m)
6n	0.78 (6H, t, 7 Hz); 0.90 (3H, s); 1.18 (3H, s); 1.31 (3H, s); 0.95–1.95 (10H, m)
6o	0.89 (9H, s and m); 1.17 (3H, s); 1.27 (3H, s); 0.95–1.95 (14H, m)

alumina, eluting with chloroform. Evaporation of solvent provided azides **6** which were purified (in the case of diastereomers also separated) by flash chromatography on silica gel, eluting with light petroleum ether.

Procedure B:

Boron trifluoride etherate (12 mmol) was added dropwise to a stirred solution of cyclohexanol **5** (10 mmol) and trimethylsilyl azide (12 mmol) in benzene (20 mL). After being stirred for 24 h at room temperature the mixture was poured into water (50 mL). The organic phase was separated and washed with saturated aqueous $NaHCO_3$ (20 mL) and brine (20 mL). The solution was dried over $MgSO_4$, filtered and concentrated. The crude product was purified (in the case of diastereomers also separated) by flash chromatography on silica gel, eluting with light petroleum ether.

The yields of cyclohexyl azides **6** are listed in *table IV*. The ^{1}H-NMR spectral data for cyclohexyl azides **6a–6o** are given in *table IX*. 1-Methylcyclohexyl azide **6p** is a known compound [8].

5.1.5. General procedure for cyclohexylamines **2**

A solution of cyclohexyl azide **6** in ether was added dropwise to a stirred suspension of lithium aluminum hydride (4 equivalents) in ether, which was cooled in an ice bath. The reaction mixture was stirred at room temperature for 5 h. Residual lithium aluminium hydride was carefully destroyed with water, the aqueous layer separated and was extracted twice with ether. The combined ethereal phases were washed with brine, dried over NaOH, filtered and evaporated. The product obtained was treated with HCl without subsequent characterization. The amine hydrochloride was prepared either by passing of HCl gas through the amine solution in hexane or by addition of a 1 N HCl solution in ether to the amine solution. In both cases the solvent was removed after HCl addition, the residue treated with hexane or acetonitrile and the crystalline product filtered off to give **2** with excellent purity. The yields of cyclohexylamines **2** are listed in *table V*. The ^{1}H-NMR spectral data for cyclohexylamines **2a–2o** are given in *table X*. 1-Methylcyclohexylamine **2p** is a known compound [30].

Acknowledgements

We wish to thank Dr J. Popelis for recording NMR spectra.

Table X. ^{1}H-NMR spectra of cyclohexylamines 2*.

Compound	M.p. (°C)	^{1}H-NMR ($CDCl_3$, TMS) δ, ppm
2a-*ax*	> 250 (subl.)	0.89 (3H, d, 6.5 Hz); 0.7–1.0 (2H, m); 1.2–1.35 (1H, m) 1.45 (3H, s); 1.6–2.1 (6H, m); 8.3 (3H, br s)
2a-*eq*	200–202	0.91 (3H, d, 6.4 Hz); 0.85–1.0 (1H, m); 1.47 (3H, s); 1.15–1.75 (6H, m); 1.94 (2H, m); 8.3 (3H, br s)
2b-*ax*	> 250 (subl.)	0.88 (3H, t, 7.5 Hz); 0.7–1.0 (2H, m); 1.1–1.35 (3H, m); 1.46 (3H, s); 1.6–1.9 (4H, m); 2.0–2.15 (2H, m); 8.35 (3H, br s)
2b-*eq*	179–181	0.87 (3H, t, 7 Hz); 1.45 (3H, s); 0.8–2.0 (11H, m); 8.3 (3H, br s)
2c-*ax*	> 250 (subl.)	0.87 (3H, t, 7.3 Hz); 0.7–1.0 (2H, m); 1.05–1.4 (5H, m); 1.45 (3H, s); 1.55–1.7 (1H, m); 1.75–1.95 (3H, m); 2.0–2.1 (2H, m); 8.3 (3H, br s)
2c-*eq*	181–182	0.85 (3H, t, 7.1 Hz); 0.8–0.9 (1H, m); 1.47 (3H, s);1.15–1.5 (7H, m); 1.6–1.8 (3H, m); 1.9–2.0 (2H, m); 8.3 (3H, br s)
2d	230–231	0.96 (3H, s); 1.06 (3H, s); 1.15–1.40 (2H, m); 1.50 (3H, s); 1.5–1.85 (6H, m); 8.25 (3H, br s)
2e-*ax*	> 280	0.4–0.6 (1H, m); 0.90 (6H, d, 6.5 Hz); 0.8–1.1 (2H, m); 1.44 (3H, s); 1.6–2.15 (5H, m); 8.3 (3H, br s)
2e-*eq*	237–238	0.45–0.75 (1H, m); 0.90 (6H, d, 5 Hz); 1.47 (3H, s); 1.2–1.7 (6H, m); 1.94 (2H, d, 11.5); 8.3 (3H, br s)
2f-*ax*	> 240	0.72 (1H, t, 12.5 Hz); 0.90 and 0.91 (total 6H, d, 6.5 Hz and s); 0.85–1.0 (1H, m); 1.16 (1H d, 14.8 Hz); 1.23 (3H, s); 1.45 (3H, s); 1.4–1.55 (1H, m); 1.85–2.0 (2H, m); 2.1 (1H, m); 8.2 (3H, br s)
2f-*eq*	> 240	0.96, 1.0 and 1.04 (total 9H, d, 6 Hz, s and s); 0.9–1.1 (1H, m); 1.37 (1H, t, 12 Hz); 1.44 (1H, d, 13 Hz); 1.61 (3H, s); 1.6–1.95 (3H, m); 2.02 (1H, d, 12 Hz) 8.25 (3H, br s)
2g-*ax*	250–253	0.67 (1H, t, 13 Hz); 0.84 (3H, s); 0.85–0.95 (m, 6H); 1.07 (1H, d, 15.5 Hz); 1.48 (3H, s); 1.5–1.8 (4H, m); 1.9–2.1 (3H, m); 8.15 (3H, br s)
2g-*eq*	228–231	0.83 (3H, t, 7.5 Hz); 0.88 (3H, s); 0.91 (3H, d, 6.5 Hz); 0.8–0.95 (1H, m); 1.55 (3H, s); 1.15–1.80 (6H, m); 1.9–2.0 (2H, m); 8.3 (3H, br s)
2h-*ax*	167–168	0.61 (1H, t, 13 Hz); 0.86 (3H, s); 0.89 (3H, d, 6 Hz); 0.85–1.0 (1H, m); 1.00 (3H, t, 7 Hz); 1.13 (1H, d, 15.5 Hz); 1.51 (3H, s); 1.15–1.75 (5H, m); 1.39 (1H, m); 1.95 (1H, d, 15.5 Hz); 2.11 (1H, d, 14.5 Hz); 8.2 (3H, br s)
2h-*eq*	237–238	0.8–0.95 (10H, m); 1.54 (3H, s); 1.1–1.8 (8H, m); 1.97 (2H, d, 13 Hz); 8.3 (3H, br s)
2i-*ax*	255–257	0.72 (1H, t, 13 Hz); 0.91 (3H, t, 7.5 Hz); 0.92 (3H, s); 0.8–0.95 (1H, m); 1.23 (3H, s); 1.1–1.3 (3H, m); 1.46 (3H, s); 1.51 (1H, d, 13 Hz); 1.85–2.0 (2H, m); 2.03 (1H, d, 15 Hz); 8.3 (3H, br s)
2i-*eq*	216–218	0.88 (3H, t, 7.5 Hz); 0.8–0.95 (1H, m); 0.96 (3H, s.); 0.98 (3H, s); 1.2–1.35 (3H, m); 1.56 (3H, s); 1.4–1.56 (3H, m); 1.83 (1H, d, 13 Hz); 2.01 (1H, d, 12 Hz); 8.3 (3H, br s)
2j-*ax*	218–221	0.72 (1H, t, 13 Hz); 0.89 (3H, t, 7 Hz); 0.92 (3H, s); 0.85–0.9 (1H, m); 1.23 (3H, s); 1.45 (3H, s); 1.0–2.1 (9H, m); 8.2 (3H, br s)
2j-*eq*	200–203	0.86 (3H, t, 7 Hz); 0.8–0.95 (1H, m); 0.95 (3H, s); 0.98 (3H, s); 1.55 (3H, s); 1.1–1.7 (8H, m); 1.83 (1H, d, 13 Hz); 1.99 (1H, d, 12 Hz); 8.3 (3H, br s)
2k	235–237	1.02 (6H, s) and 1.07 (6H, s); 1.26 (2H, br s); 1.62 (3H, s); 1.71 (4H, br s);
2l	215–218	1.03 (3H, s) 1.06 (3H, s); 1.09 (3H, t, 7.5 Hz); 1.30 (2H, br s); 1.63 and 1.78 (total 4H, both d, 14 Hz); 1.97 (2H, q, 7 Hz); 8.15 (3H, br s)
2m	> 280	0.93 (3H, t, 7 Hz); 1.01 (6H, s); 1.04 (6H, s); 1.29 (2H, br s); 1.35–2.0 (4H, m); 1.70 (4H, m); 8.2 (3H, br s)
2n	99–102	0.75–0.85 (6H, m); 1.04 (3H, s); 1.05 (3H, s); 1.19 (1H, d, 14 Hz); 1.25–1.50 (3H, m); 1.60 (3H, s); 1.67 and 1.75 (total 4H, both d, 14 Hz); 8.25 (3H, br s)
2o	167–169	0.83–0.89 (6H, m); 1.03 (3H, s); 1.05 (3H, s); 1.15–1.45 (10H, m); 1.57 (2H, d, 14.5 Hz); 1.61 (3H, s); 1.77 (2H, d, 14 Hz); 8.2 (3H, br s)

* 1, *trans*-3-Dimethylcyclohexylamine hydrochloride **2a-*ax***: ^{13}C-NMR ($CDCl_3$, 50 MHz) δ: 21.75 (C-5); 23.02 (3-CH_3); 27.99 (C-3); 28.67 (1-CH_3); 34.72 (C-4); 36.63 (C-6); 45.50 (C-2); 56.20 (C-1); 1, *cis*-3- dimethylcyclohexylamine hydrochloride semihydrate **2a-*eq***: ^{13}C-NMR ($CDCl_3$, 50 MHz) δ: 22.9–23.05 (C-5, 3-CH_3, 1-CH_3); 29.71 (C-3); 34.68 (C-4); 36.87 (C-6); 45.45 (C-2); 56.81 (C-1); 1-methyl, *trans*-3-ethylcyclohexylamine hydrochloride **2b-*ax***; 1-methyl, *cis*-3-ethylcyclohexylamine hydrochloride **2b-*eq***; 1-methyl, *trans*-3-propylcyclohexylamine hydrochloride **2c-*ax***; 1-methyl, *cis*-3-propylcyclohexylamine hydrochloride **2c-*eq***; 1,3,3-trimethylcyclohexylamine hydrochloride **2d**; 1, *trans*-3, *trans*-5-trimethylcyclohexylamine hydrochloride **2e-*ax***; 1, *cis*-3, *cis*-5-trimethylcyclohexylamine hydrochloride hydrate **2e-*eq***; 1,3,3, *trans*-5-tetramethylcyclohexylamine hydrochloride **2f-*ax***; 1,3,3, *cis*-5-tetramethylcyclohexylamine hydrochloride semihydrate **2f-*eq***; *cis*-3-ethyl-1, trans-3, trans-5-trimethylcyclohexylamine hydrochloride **2g-*ax***; *trans*-3-ethyl-1, cis-3, cis-5-trimethylcyclohexylamine hydrochloride **2g-*eq***; *cis*-3-propyl-1, trans-3, trans-5-trimethylcyclohexylamine hydrochloride **2h-*ax***; *trans*-3-propyl-1, cis-3, cis-5-trimethylcyclohexylamine hydrochloride **2h-*eq***; 1,3,3-trimethyl-*trans*-5-ethylcyclohexylamine hydrochloride **2i-*ax***; 1,3,3-trimethyl-*cis*-5-ethylcyclohexylamine hydrochloride semihydrate **2i-*eq***; 1,3,3-trimethyl-*trans*-5-propylcyclohexylamine hydrochloride **2j-*ax***; 1,3,3-trimethyl-*cis*-5-propylcyclohexylamine hydrochloride **2j-*eq***; 1,3,3,5,5-pentamethylcyclohexylamine hydrochloride **2k**; 1-ethyl-3,3,5,5-tetramethylcyclohexylamine hydrochloride hydrate **2l**; 1-propyl-3,3,5,5-tetramethylcyclohexylamine **2m**; 3,3-diethyl-1,5,5-trimethylcyclohexylamine hydrate **2n**; 3,3-Dipropyl-1,5,5-trimethylcyclohexylamine **2o**.

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2. Pielikums

US006034134A

United States Patent [19]

Gold et al.

[11] Patent Number: 6,034,134

[45] Date of Patent: Mar. 7, 2000

[54] 1-AMINO-ALKYLCYCLOHEXANE NMDA RECEPTOR ANTAGONISTS

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[21] Appl. No.: 09/141,381

[22] Filed: Aug. 27, 1998

Related U.S. Application Data

[63] Continuation-in-part of application No. 08/885,944, Jun. 30, 1997, abandoned.

[51] Int. Cl.[7] A61K 33/00

[52] U.S. Cl. 514/579; 514/659; 564/454; 564/455; 564/462

[58] Field of Search 564/454, 455, 564/462; 514/579, 659

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[57] ABSTRACT

Certain 1-aminoalkylcyclohexanes are systemically-active uncompetitive NMDA receptor antagonists having rapid blocking/unblocking kinetics and strong voltage-dependency and are therefore useful in the alleviation of conditions resulting from disturbances of glutamatergic transmission giving them a wide range of utility in the treatment of CNS disorders involving the same, as well as in non-NMDA indications, due to their immunomodulatory, antimalarial, anti-Borna virus, and anti-Hepatitis C activities and utilities. Pharmaceutical compositions thereof and a method-of-treating conditions which are alleviated by the employment of an NMDA receptor antagonist, as well as the aforementioned non-NMDA indications, and a method for the preparation of the active 1-aminoalkylcyclohexane compounds involved.

22 Claims, 2 Drawing Sheets

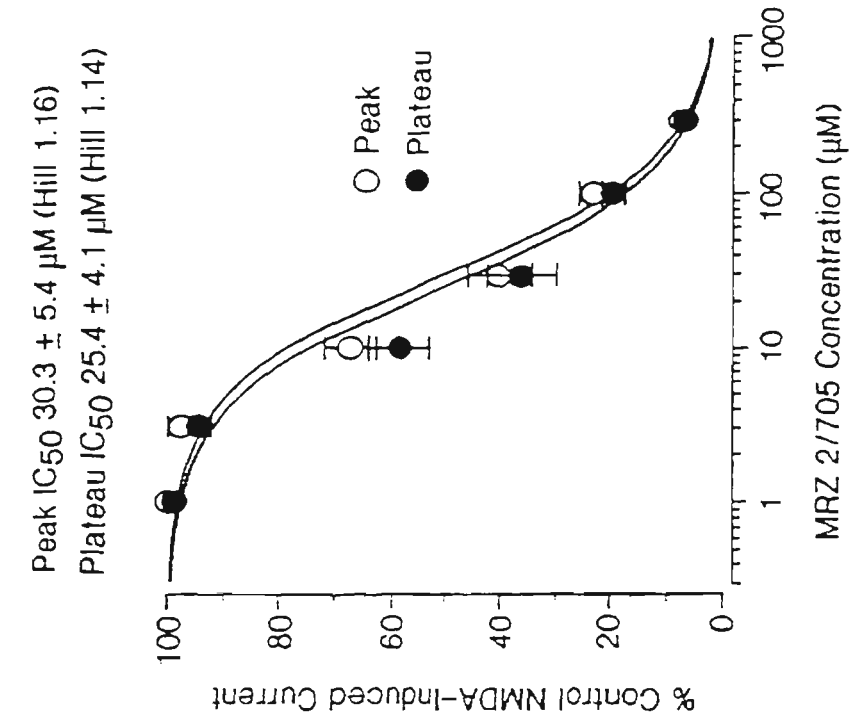

Peak IC50 30.3 ± 5.4 µM (Hill 1.16)
Plateau IC50 25.4 ± 4.1 µM (Hill 1.14)
O Peak
● Plateau
% Control NMDA-Induced Current
100
80
60
40
20
0
1
10
100
1000
MRZ 2/705 Concentration (µM)

FIG. 1B

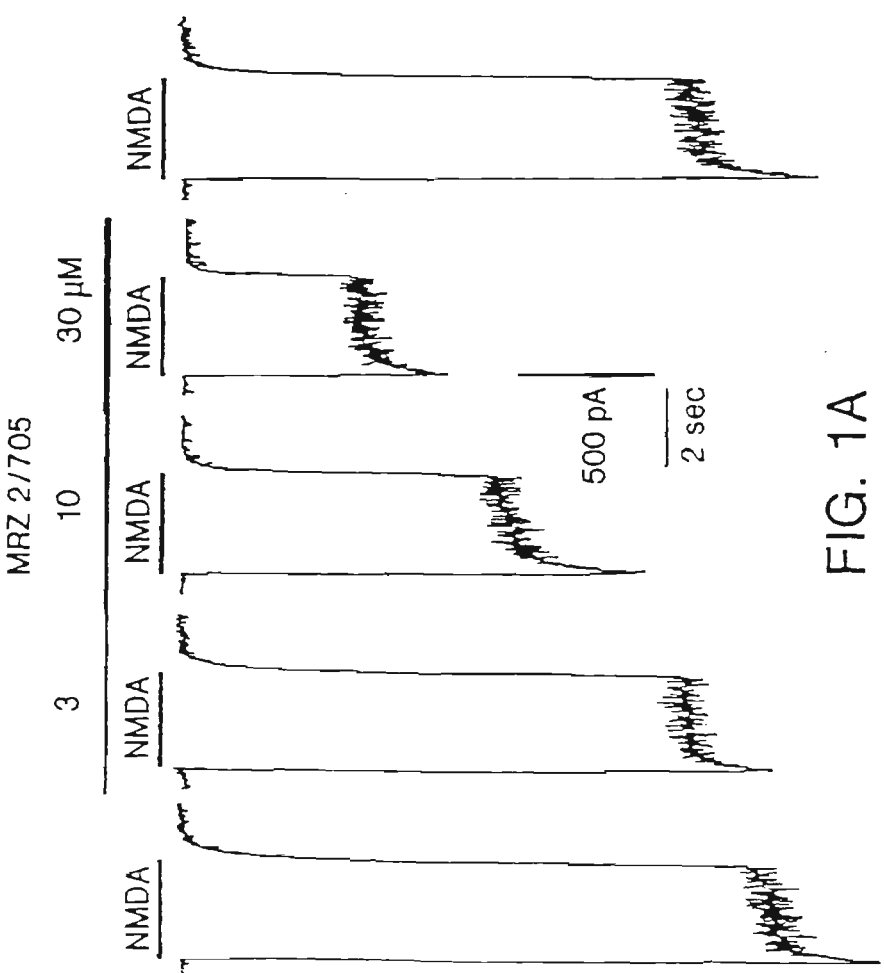

MRZ 2/705
3
10
30 µM
NMDA
NMDA
NMDA
NMDA
500 pA
2 sec

FIG. 1A

1-AMINO-ALKYLCYCLOHEXANE NMDA RECEPTOR ANTAGONISTS

The present application is a continuation-in-part of our prior-filed copending application Ser. No. 08/885,944 filed Jun. 30, 1997, now abandoned.

BACKGROUND OF THE INVENTION

1. Field of the Invention

1-Amino-alkylcyclohexane compounds which are systemically-active as NMDA receptor antagonists, pharmaceutical compositions comprising the same, method of preparation thereof, and method of treating CNS disorders which involve disturbances of glutamatergic transmission therewith.

2. Prior Art

Antagonism of glutamate receptors of the N-methyl-D-aspartate (NMDA) type has a potentially wide range of therapeutic applications [19]. Functional inhibition of NMDA receptors can be achieved through actions at different recognition sites such as the primary transmitter site, strychnine-insensitiveglycine site (glycine$_B$), polyamine site, and phencyclidine site located inside the cation channel. The NMDA receptor channel blockers act in an uncompetitive "use-dependent" manner, meaning that they usually only block the channel in the open state. This use-dependence has been interpreted by many to mean that stronger activation of the receptor should lead to a greater degree of antagonism. Such a mode of action has further been taken to imply that this class of antagonist may be particularly useful when overactivation of NMDA receptors can be expected, such as in epilepsy, ischaemia, and trauma. However, initial clinical experience with the selective, high affinity, strongly use-dependent uncompetitive NMDA receptor antagonist (+)-5-methyl-10,11-dihydro-5H-dibenzocyclohepten-5,10-imine maleate ((+)-MK-801) has been disappointing. Namely, therapeutic efficacy in epilepsy was poor while some psychotropic side effects were apparent at therapeutic doses. These observations, together with the fact that phencyclidine abusers experience similar psychotropic symptoms, has led to the conclusion that uncompetitive antagonism of NMDA receptors may not be a promising therapeutic approach.

However, the use of more elaborate electrophysiological methods indicates that there is no equality between different uncompetitive antagonists since factors such as the speed of receptor blockade (on-off kinetics) and the voltage-dependence of this effect may determine the pharmacodynamic features in vivo, i.e., therapeutic safety as well. Paradoxically, agents with low to moderate, rather than high, affinity may be desirable. Such findings triggered a reconsideration of the concept of uncompetitive antagonism of NMDA receptors in drug development [19, 22]. At present, many such agents are at different stages of development, e.g., carvedilol, ADCI, ES 242S, remacemide, felbamate, and budipine. On the other hand, uncompetitive NMDA receptor antagonists, such as amantadine and memantine—which fulfill the above criteria—have been used clinically for several years in the treatment of Parkinson's disease and dementia respectively, and do indeed rarely produce side effects at the therapeutic doses used in their respective indications.

In view of the above mentioned evidence, we have developed a series of novel uncompetitive NMDA receptor antagonists based on the 1-aminoalkylcyclohexane structure. The present study was devoted to compare the NMDA receptor antagonistic properties of these 1-aminoalkylcyclohexane derivatives in receptor-binding assays, patch clamp experiments, excitotoxicity in vitro, three convulsion models, and two models of motor impairment. The substitutions of these 1-aminoalkylcyclohexanes are detailed in Table 6.

THE PRESENT INVENTION

It has now been found that certain 1-aminoalkylcyclohexanes have pronounced and unpredictable NMDA receptor antagonistic activity. Owing to the aforementioned property, the substances are suited for the treatment of a wide range of CNS disorders which involve disturbances of the glutamatergic transmission, preferably in the form of a pharmaceutical composition thereof wherein they are present together with one or more pharmaceutically-acceptable diluents, carriers, or excipients.

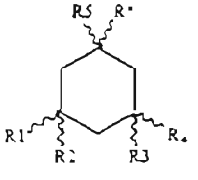
OBJECTS OF THE INVENTION

It is an object of the present invention to provide novel pharmaceutical compounds which are 1-aminoalkylcyclohexane NMDA receptor antagonists and pharmaceutical compositions thereof. It is a further object of the invention to provide a novel method of treating, eliminating, alleviating, palliating, or ameliorating undesirable CNS disorders which involve disturbances of glutamatergic transmission by the employment of such a compound of the invention or a pharmaceutical composition containing the same. An additional object of the invention is the provision of a process for producing the said 1-aminoalkylcyclohexane active principles. Yet additional objects will become apparent hereinafter, and still further objects will be apparent to one skilled in the art.

SUMMARY OF THE INVENTION

What we therefore believe to be comprised by our invention may be summarized inter alia in the following words:

A 1-aminoalkylcyclohexane compound selected from the group consisting of those of the formula



wherein R^6 is $—(CH_2)_n—(CR^6R^7)_m—NR^8R^9$

wherein n+m=0, 1, or 2

wherein R^1 through R^7 are independently selected from the group consisting of hydrogen and lower-alkyl (1–6C), at least R^1, R^4, and R^5 being lower-alkyl, and wherein R^8 and R^9 are independently selected from hydrogen and lower-alkyl (1–6C) or together represent lower-alkylene $—(CH_2)_x—$ wherein x is 2 to 5, inclusive, and enantiomers, optical isomers, hydrates, and pharmaceutically-acceptable salts thereof;

such a compound wherein R^1 through R^5 are methyl;

such a compound wherein R^1 is ethyl;

such a compound wherein R^2 is ethyl;

such a compound wherein R^3 is ethyl;

such a compound wherein R^4 is ethyl;

such a compound wherein R^5 is ethyl;

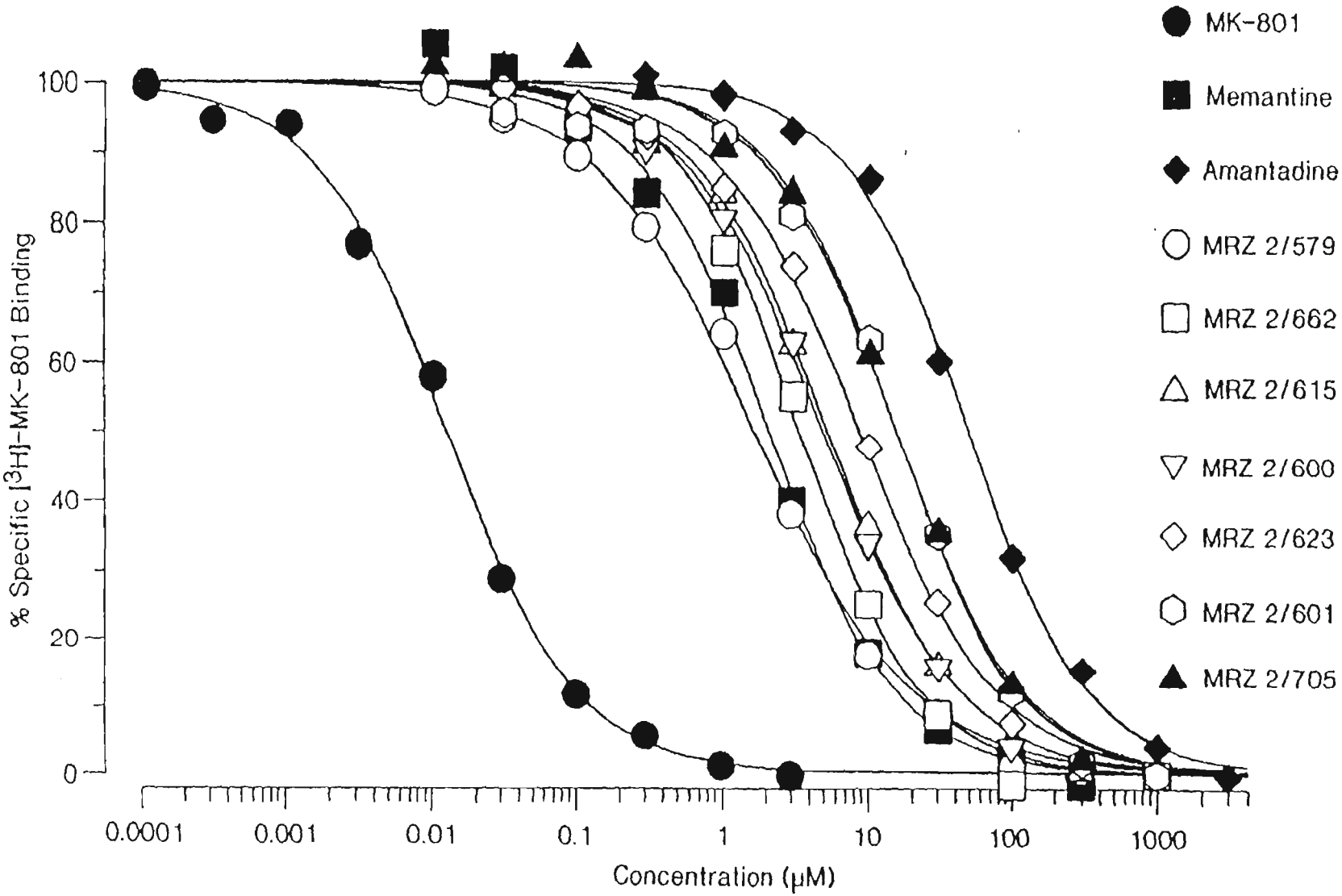
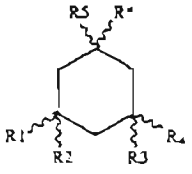

MK-801
Memantine
Amantadine
MRZ 2/579
MRZ 2/662
MRZ 2/615
MRZ 2/600
MRZ 2/623
MRZ 2/601
MRZ 2/705
% Specific [3H]-MK-801 Binding
100
80
60
40
20
0
0.0001
0.001
0.01
0.1
1
10
100
1000
Concentration (μM)

FIG. 2

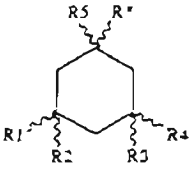
such a compound wherein R^5 is propyl;
such a compound wherein R^6 or R^7 is methyl;
such a compound wherein R^6 or R^7 is ethyl; and
such a compound wherein the compound is selected from the group consisting of
1-amino-1,3,5-trimethylcyclohexane.
1-amino-1(trans),3(trans),5-trimethylcyclohexane.
1-amino-1(cis),3(cis),5-trimethylcyclohexane.
1-amino-1,3,3,5-tetramethylcyclohexane.
1-amino-1,3,3,5,5-pentamethylcyclohexane.
1-amino-1,3,5,5-tetramethyl-3-ethylcyclohexane.
1-amino-1,5,5-trimethyl-3,3-diethylcyclohexane.
1-amino-1,5,5-trimethyl-cis-3-ethylcyclohexane.
1-amino-(1S,5S)cis-3-ethyl-1,5,5-trimethylcyclohexane.
1-amino-1,5,5-trimethyl-trans-3-ethylcyclohexane.
1-amino-(1R,5S)trans-3-ethyl-1,5,5-trimethylcyclohexane.
1-amino-1-ethyl-3,3,5,5-tetramethylcyclohexane.
1-amino-1-propyl-3,3,5,5-tetramethylcyclohexane.
N-methyl-1-amino-1,3,3,5,5-pentamethylcyclohexane. N-ethyl-1-amino-1,3,3,5,5-pentamethylcyclohexane. and N-(1,3,3,5,5-pentamethylcyclohexyl) pyrrolidine, and hydrates and pharmaceutically-acceptable salts of any of the foregoing.

Moreover, a method-of-treating a living animal for alleviation of a condition which is alleviated by an NMDA receptor antagonist, or for its immunomodulatory, antimalarial, anti-Borna virus, or anti-Hepatitis C effect, comprising the step of administering to the said living animal an amount of a 1-aminoalkylcyclohexane compound selected from the group consisting of those of the formula



wherein R^* is $-(CH_2)_n-(CR^6R^7)_m-NR^8R^9$
wherein n+m=0, 1, or 2
wherein R^1 through R^7 are independently selected from the group consisting of hydrogen and lower-alkyl (1–6C), wherein R^8 and R^9 are independently selected from hydrogen and lower-alkyl (1–6C) or together represent lower-alkylene $-(CH_2)_x-$ wherein x is 2 to 5, inclusive, and optical isomers, enantiomers, hydrates, and pharmaceutically-acceptable salts thereof, which is effective for the said purpose:
such a method wherein R^1 through R^5 are methyl;
such a method wherein R^1 is ethyl;
such a method wherein R^2 is ethyl;
such a method wherein R^3 is ethyl;
such a method wherein R^4 is ethyl;
such a method wherein R^5 is ethyl;
such a method wherein R^5 is propyl;
such a method wherein R^6 or R^7 is methyl;
such a method wherein R^6 or R^7 is ethyl; and
such a method wherein the compound is selected from the group consisting of
1-amino-1,3,5-trimethylcyclohexane.
1-amino-1(trans),3(trans),5-trimethylcyclohexane.
1-amino-1(cis),3(cis),5-trimethylcyclohexane.
1-amino-1,3,3,5-tetramethylcyclohexane.
1-amino-1,3,3,5,5-pentamethylcyclohexane.
1-amino-1,3,5,5-tetramethyl-3-ethylcyclohexane.
1-amino-1,5,5-trimethyl-3,3-diethylcyclohexane.
1-amino-1,5,5-trimethyl-cis-3-ethylcyclohexane.
1-amino-(1S,5S)cis-3-ethyl-1,5,5-trimethylcyclohexane.
1-amino-1,5,5-trimethyl-trans-3-ethylcyclohexane.
1-amino-(1R,5S)trans-3-ethyl-1,5,5-trimethylcyclohexane.
1-amino-1-ethyl-3,3,5,5-tetramethylcyclohexane.
1-amino-1-propyl-3,3,5,5-tetramethylcyclohexane.
N-methyl-1-amino-1,3,3,5,5-pentamethylcyclohexane,
N-ethyl-1-amino-1,3,3,5,5-pentamethylcyclohexane, and
N-(1,3,3,5,5-pentamethylcyclohexyl) pyrrolidine, and hydrates and pharmaceutically-acceptable salts of any of the foregoing; and
such a method wherein the compound is administered in the form of a pharmaceutical composition thereof comprising the compound in combination with one or more pharmaceutically-acceptable diluents, excipients, or carriers.

Further, an NMDA-receptor antagonist pharmaceutical composition comprising an effective NMDA-receptor antagonistic amount, or an effective immunomodulatory, antimalarial, anti-Borna virus, or anti-Hepatitis C amount, of a 1-aminoalkylcyclohexane compound selected from the group consisting of those of the formula



wherein R^* is $-(CH_2)_n-(CR^6R^7)_m-NR^8R^9$
wherein n+m=0, 1, or 2
wherein R^1 through R^7 are independently selected from the group consisting of hydrogen and lower-alkyl (1–6C), at least R^1, R^4, and R^5 being lower-alkyl, and wherein R^8 and R^9 are independently selected from hydrogen and lower-alkyl (1–6C) or together represent lower-alkylene $-(CH_2)_x-$ wherein x is 2 to 5, inclusive, and optical isomers, enantiomers, hydrates, and pharmaceutically-acceptable salts thereof, in combination with one or more pharmaceutically-acceptable diluents, excipients, or carriers;
such a pharmaceutical composition wherein R^1 through R^5 are methyl;
such a pharmaceutical composition wherein R^1 is ethyl;
such a pharmaceutical composition wherein R^2 is ethyl;
such a pharmaceutical composition wherein R^3 is ethyl;
such a pharmaceutical composition wherein R^4 is ethyl;
such a pharmaceutical composition wherein R^5 is ethyl;
such a pharmaceutical composition wherein R^5 is propyl;
such a pharmaceutical composition wherein R^6 or R^7 is methyl;
such a pharmaceutical composition wherein R^6 or R^7 is ethyl;
such a pharmaceutical composition wherein the compound is selected from the group consisting of
1-amino-1,3,5-trimethylcyclohexane.
1-amino-1(trans),3(trans),5-trimethylcyclohexane.

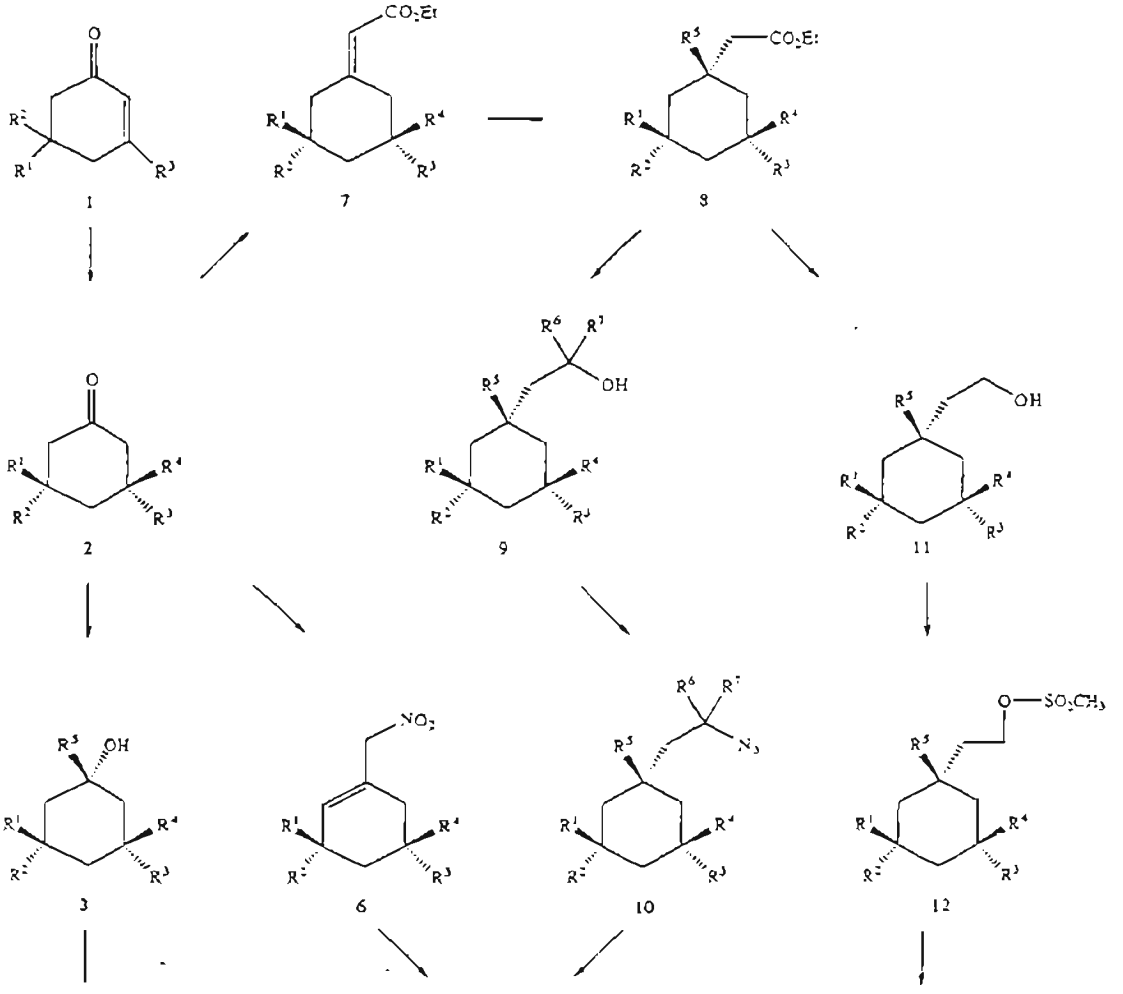
1-amino-1(cis),3(cis),5-trimethylcyclohexane.
1-amino-1,3,3,5-tetramethylcyclohexane.
1-amino-1,3,3,5,5-pentamethylcyclohexane.
1-amino-1,3,5,5-tetramethyl-3-ethylcyclohexane.
1-amino-1,5,5-trimethyl-3,3-diethylcyclohexane.
1-amino-1,5,5-trimethyl-cis-3-ethylcyclohexane.
1-amino-(1S,5S)cis-3-ethyl-1,5,5-trimethylcyclohexane.
1-amino-1,5,5-trimethyl-trans-3-ethylcyclohexane.
1-amino-(1R,5S)trans-3-ethyl-1,5,5-trimethylcyclohexane.
1-amino-1-ethyl-3,3,5,5-tetramethylcyclohexane.
1-amino-1-propyl-3,3,5,5-tetramethylcyclohexane.
N-methyl-1-amino-1,3,3,5,5-pentamethylcyclohexane.
N-ethyl-1-amino-1,3,3,5,5-pentamethylcyclohexane, and
N-(1,3,3,5,5-pentamethylcyclohexyl) pyrrolidine, and hydrates and pharmaceutically-acceptable salts of any of the foregoing.

DETAILED DESCRIPTION OF THE INVENTION

The following details and detailed Examples are given by way of illustration only, and are not to be construed as limiting.

METHODS

Chemistry



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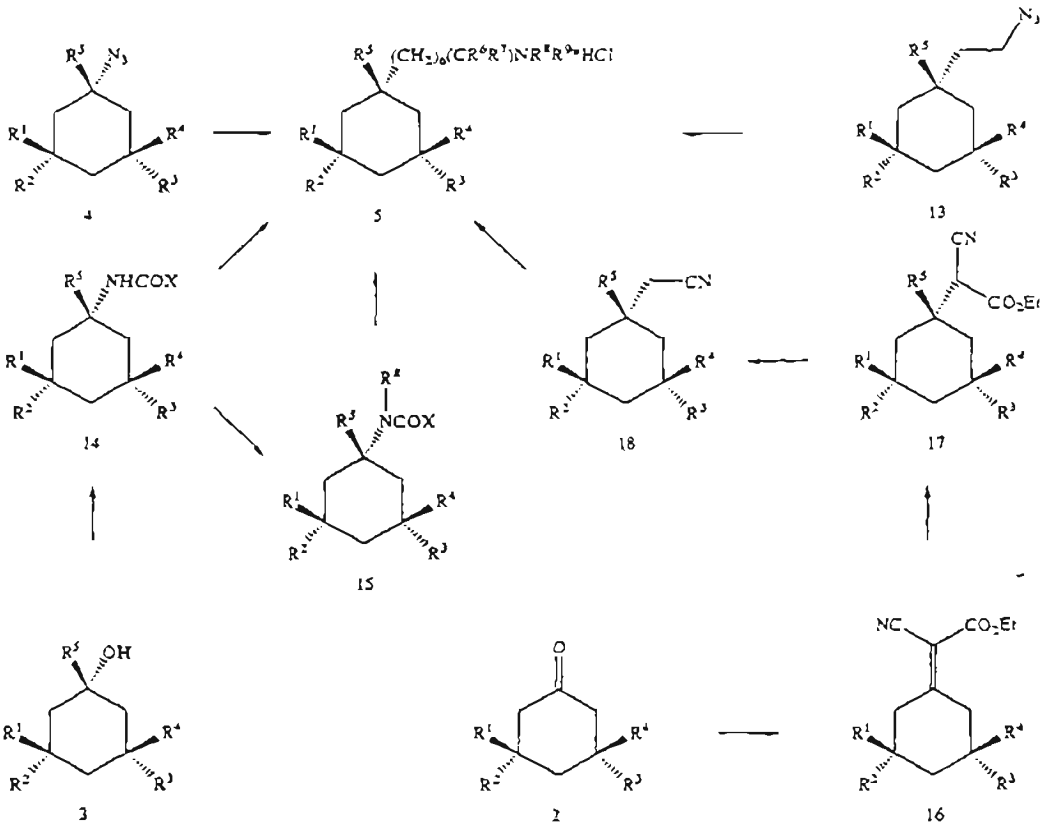

Preparation of 3-propyl-5,5-dimethyl-2-cyclohexene-1-one (1-7)

A solution of 3-ethoxy-5,5-dimethyl-2-cyclohexene-1-one [1] (5.04 g, 30 mmol) in ether was added dropwise to a stirred solution of propylmagnesium iodide prepared from 90 mg of magnesium and 90 mmol of 1-iodopropane in 60 ml of ether. After being stirred for 1 h at ambient temperature, the reaction mixture was treated with 5% H_2SO_4 solution. The organic phase was separated, washed with saline, dried over $MgSO_4$ and evaporated to give a crude oil which was separated on a silica gel column, eluting with hexane-ethyl acetate mixture. Cyclohexenone (1-7) was obtained as a colourless oil (2.0 g, 70%). ^1H NMR ($CDCl_3$, TMS) δ: 0.92 (3H, t, J=7 Hz); 1.03 (6H, s); 1.3–1.75 (2H, m); 2.16 (2H, t, J=7 Hz); 2.17 (2H, d, J=1.5 Hz); 2.21 (2H, s) and 5.87 ppm (1H, t, J=1.5 Hz).

Such known cyclohexenones 1 were used to prepare compounds 2:

1-1 (R^1=R^2=R^3=H) [commerc. available].

1-2 (R^3=Me)* [commerc. available].

1-3 (R^2=R^3=Me) [commerc. available].

1-4 (R^1=R^2=Me) [2].

1-5 (R^1=R^2=R^3=Me) [commerc. available].

1-6 (R^1=R^2=Me, R^3=Et) [3].

*R^n=H, if omitted.

Other starting materials 1 are prepared in the same or similar manner.

General procedure for preparation of cyclohexanones 2.

Anhydrous copper (I) chloride (7.5 mmol) was added to a cooled solution of alkylmagnesium iodide (15–18 mmol) in ether. The mixture was stirred in an inert atmosphere for 5 minutes and a solution of 2-cyclohexene-1-one 1 (10 mmol) in ether was added dropwise keeping the temperature below −5° C. After the addition of ketone was completed, the reaction mixture was stirred for 1 hour and carefully neutralized with saturated aqueous NH_4Cl solution. Traditional workup for Grignard reactions gave crude material which was separated on a silica gel column, eluting with a petroleum ether—ethyl acetate mixture. The cyclohexanones 2 were obtained as oils.

Yields and ^1H NMR spectral data of compounds 2 are given in Table 1.

Such known cyclohexanones 2 were used to prepare compounds 3.

2-1 (R^4=Me)* [commerc. available].

2-2 (R^4=Et) [4].

2-3 (R^4=Pr) [5].

2-4 (R^3=R^4=Me) [6].

2-5 (R^3=Me, R^4=Et) [7].

2-6 (R^3=Me, R^4=Pr) [8].

2-7 (R^1=R^4=Me) [9].

2-8 (R^2=R^3=R^4=Me) [10].

2-9 (R^2=R^3=Me, R^4=Et) [11].

2-13 (R^1=R^2=R^3=R^4=Me) [commerc. available].

2-14 (R^1=R^2=R^3=Me, R^4=Et) [10].

2-15 (R^1=R^2=R^3=Me, R^4=Pr) [10].

*Rn=H, if omitted.

Other intermediate cyclohexanones 2 are prepared in the same or a similar manner. Cyclohexanones 2 were used to prepare compounds 3:

General Procedure for preparation of alkylcyclohexanols 3.

An etheral solution of alkylmagnesium iodide (3-4 equivalents) was added dropwise to a cooled solution of cyclohexanone 2 in ether. The mixture was stirred for 1 hour at ambient temperature and carefully destroyed with saturated aqueous ammonium chloride. Traditional workup for Grignard reactions gave mixtures of diastereomeric alcohols 3, which were separated on a silica gel column eluting with petroleum ether—ethyl acetate.

Yields and ^{1}H NMR spectral data of compounds 3 are to given in Table 2.

Such known cyclohexanols 3 were used to prepare compounds 4:

3-1 ($(R^3)(R^4)=R^5=Me$)* [9]. i.e., R^3 or R^4 and R^5 are Me.

3-4 ($R^3=R^4=R^5=Me$) [12].

3-5 ($R^3=R^5=Me$, $R^4=Et$) [13].

3-7 ($R^1=R^4=R^5=Me$) [14].

3-8 ($R^1=R^3=R^4=R^5=Me$) [10].

3-13 ($R^1=R^2=R^3=R^4=R^5=Me$) [10].

3-14 ($R^1=R^2=R^3=R^4=Me$, $R^5=Et$) [15].

*R^n=H, if omitted.

Other intermediate cyclohexenols 3 are prepared in the same or a similar manner.

General procedure for preparation of 1-alkyl-1-azidocyclohexanes 4.

The alcohol 3 was mixed with 1.7–2 N hydrazoic acid (10–13 equivalents) solution in chloroform and cooled in an ice bath. A solution of $TiCl_4$ (1.2 equivalents) in chloroform was added dropwise while temperature was maintained below 5° C. The mixture was stirred at room temperature for 24 hours and passed down a column of alumina, eluting with chloroform. Evaporation of solvent provided diastereomeric azides 4 which were purified by flash chromatography on silica gel, eluting with light petroleum ether.

Yields and ^{1}H NMR spectral data of compounds 4 are given in Table 3.

Other intermediate 1-alkyl-1-azidocyclohexanes 4 are prepared in the same or a similar manner.

Preparation of 1-nitromethyl-3,3,5,5-tetramethylcyclohexene (6).

A solution of 3,3,5,5-tetramethylcyclohexanone (2-13) (1.54 g, 10 mmol) and ethylenediamine (60 mg) in nitromethane (45 ml) was refluxed in argon atmosphere for 25 h. Excess of nitromethane was then removed in vacuo and the residue was purified by flash chromatography on silica gel, eluting with hexane—ethyl acetate (6:1). 1.2 g (61%) of 6 was obtained as an oil.

^{1}H NMR ($CDCl_3$, TMS) δ 0.96 and 1.03 (total 12H, both s, cyclohexane 3,5-CH_3); 1.34 (2H, s, 4-CH_2); 1.82 (2H, br s, 6—CH_2); 4.80 (2H, s, CH_2NO_2) and 5.64 ppm (1H, br s, C=C—H).

Preparation of ethyl 3,3,5,5-tetramethylcyclohexylideneacetate (7).

To a stirred solution of triethyl phosphonoacetate (49.32 g, 0.22 mol) in dry THF (180 ml) under argon NaH (8.8 g, 0.22 mol, 60% suspension in mineral oil) was added in small portions while cooling with ice water. Stirring was continued for 1 h at room temperature, then a solution of 3,3,5,5-tetramethylcyclohexanone (2-13) (30.85 g, 0.2 mol) was added over 10 min and the resulting mixture was refluxed for 22 h. It was then poured onto ice (400 g), the product was extracted with ether (4*150 ml) and the solution dried over $MgSO_4$. After concentration in vacuo an oily residue was distilled at 145° C. (11 mm) to give 36.8 g (86%) of 6 as an oil.

^{1}H NMR ($CDCl_3$, TMS) δ 0.96 and 0.98 (total 12H, both s, cyclohexane 3,5-CH_3); 1.27 (3H, t, CH_3-ethyl); 1.33 (2H, m, cyclohexane 4-CH_2); 1.95 and 2.65 (total 4H, both s, cyclohexane 2,6-CH_2); 4.14 (2H, q, CH_2-ethyl) and 5.69 ppm (1H, s, =C—H).

Preparation of ethyl 3,3,5,5-tetramethylcyclohexylacetate (8).

Ethyl 3,3,5,5-tetramethylcyclohexylideneacetate (7) (4.48 g, 20 mmol) in ethanol (100 ml) was hydrogenated over 10% Pd/C (0.22 g, 5 wt. %) at 10 atm for 18 h. Filtration through Celite™ and evaporation afforded 4.28 g (95%) of 8 as an oil.

^{1}H NMR ($CDCl_3$, TMS) δ 0.89 and 1.02 (total 12H, both s, cyclohexane 3,5-CH_3); 1.26 (3H, t, J=7 Hz, CH_3-ethyl); 0.6–1.55 (7H, m, ring protons); 2.13 (2H, m, 2-CH_2); and 4.12 ppm (2H, q, J=7 Hz, CH_2-ethyl).

Preparation of 2-methyl-(3,3,5,5-tetramethylcyclohexyl)-propan-2-ol (9).

A solution of ethyl 3,3,5,5-tetramethylcyclohexylacetate (8) (2.26 g, 10 mmol) in ether (20 ml) was added dropwise to a 2 M methylmagnesium iodide solution in ether (20 ml) over 15 min, while cooling with ice water. The mixture was refluxed for 2 h, cooled and quenched with saturated aqueous NH_4Cl. After traditional workup the product was purified on silica gel column, eluting with a mixture of hexane-ethyl acetate (20:1) to give 1.7 g (80%) of 9 as an oil.

^{1}H NMR ($CDCl_3$, TMS) δ 0.86 and 1.00 (total 12H, both s, cyclohexane 3,5-CH_3); 1.23 (6H, s, α-CH_3); 1.36 (2H, d, J=5 Hz, —CH_2—); 0.6–2.04 ppm (8H, m, ring protons and OH).

Preparation of 2-methyl-(3,3,5-tetramethylcyclohexyl)-propyl-2-azide (10).

Boron trifluoride etherate (0.77 g, 0.69 ml, 5.44 mmol) was added dropwise to a stirred solution of 2-methyl-(3,3,5,5-tetramethylcyclohexyl)-propan-2-ol (9) (0.96 g, 4.53 mmol) and trimethylsilyl azide (0.63 g, 0.72 ml, 5.44 mmol) in benzene (10 ml). After being stirred for 24 h at room temperature the mixture was poured into water (20 ml). The organic phase was separated and washed with saturated aqueous $NaHCO_3$ (10 ml) and saline (10 ml). The solution was dried over $MgSO_4$, filtered and concentrated. The crude product was purified on silica gel column, eluting with hexane to give 0.56 g (52%) of 10 as an oil. ^{1}H NMR ($CDCl_3$, TMS) δ: 0.87 and 1.01 (total 12H, both s, cyclohexane 3,5-CH_3); 1.27 (6H, s α-CH_3); 1.36 (2H, d, J=5 Hz, —CH_2—); 0.6–1.85 ppm (7H, m, ring protons).

Preparation of 2-(3,3,5,5-tetramethylcyclohexyl)-ethanol (11).

A solution of ethyl 3,3,5,5-tetramethylcyclohexylacetate 8 (1.8 g, 8.0 mmol) in ether (30 ml) was added dropwise to a stirred suspension of lithium aluminum hydride (0.9 g, 24.0 mmol) in ether (30 ml), which was cooled in an ice bath. The reaction mixture was refluxed for 3 h, cooled and residual lithium aluminum hydride was destroyed with water. The aqueous layer was separated and twice extracted with ether. The combined ether phases were washed with saline, dried over $MgSO_4$, filtered and evaporated. The crude product was purified by flash chromatography on silica gel, eluting with hexane—ethyl acetate mixture (4:1) to give 1.2 g (79%) of 11 as an oil. ^{1}H NMR ($CDCl_3$, TMS) δ: 0.89 and 1.00 (total 12H, both s, cyclohexane 3,5-CH_3); 1.44 (2H, q, J=7 Hz, 2-CH_2); 0.55–1.95 (8H, m, ring protons and OH) and 3.70 ppm (2H, t, J=7 Hz, CH_2O).

Preparation of 2-(3,3,5,5-tetramethylcyclohexyl)-ethyl methanesulfonate(12).

A solution of methanesulfonyl chloride (1.03 g, 0.7 ml, 9.0 mmol) in dry benzene (20 ml) was added to a stirred solution of 2-(3,3,5,5-tetramethylcyclohexyl)ethanol (11) (1.1 g, 6.0 mmol) and triethylamine (1.2 g, 1.7 ml, 12 mmol)

in benzene (40 ml), while cooling in an ice bath. The reaction mixture was stirred at room temperature for 3 h, then filtered through a short silica gel column, eluting with benzene. Evaporation of solvent gave 1.48 g (94%) of 12 as an oil. ^{1}H NMR ($CDCl_3$, TMS) δ: 0.88 and 0.98 (total 12H, both s, cyclohexane 3,5-CH_3); 1.62 (2H, q, J=7 Hz, 2-CH_2); 0.65–2.0 (7H, m, ring protons) 3.0 (3H, s, CH_3—SO_2) and 4.29 ppm (2H, t, J=7 Hz, CH_2O).

Preparation of 2-(3,3,5,5-tetramethylcyclohexyl)-ethylazide (13).

The mixture of sodium azide (2.27 g, 34.2 mmol), 2-(3,3,5,5-tetramethylcyclohexyl)-ethyl methanesulfonate-(12) (1.46 g, 5.57 mmol) and dimethyl sulfoxide (20 ml) was stirred at room temperature for 48 h, diluted with water (50 ml) and extracted with ether (3*30 ml). The organic phase was washed with saline (30 ml), dried over $MgSO_4$, filtered and evaporated. The crude product was purified by flash chromatography on silica gel, eluting with hexane to give 0.93 g (80%) of (13) as an oil. ^{1}H NMR ($CDCl_3$, TMS) δ: 0.87 and 0.99 (total 12H, both s, cyclohexane 3,5-CH_3); 1.47 (2H, q, J=7 Hz, 2-CH_2); 0.55–1.9 (7H, m, ring protons) and 3.31 ppm (2H, t, J=7 Hz, CH_2N_3).

Preparation of N-formyl-1,3,3,5,5-pentamethylcyclohexanamine (14-1).

To a vigorously stirred solution of 1,3,3,5,5-pentamethylcyclohexanol (3-13) (2.7 g, 15.6 mmol) and trimethylsilyl cyanide (2.36 g, 23.8 mmol) in acetic acid (2.5 ml) under argon 98% sulfuric acid (4.66 g, 47.6 mmol) was added, keeping temperature below −5° C. The mixture was stirred at room temperature for 22 h, then it was poured onto ice (100 g), neutralised with 50% NaOH solution to pH ~7 and extracted with ether (3*30 ml). The combined ether phases were washed with saline (50 ml), then dried over $MgSO_4$ and evaporated. A slightly yellow crystalline residue was treated with small amount of acetonitrile and filtered off to give 2.5 g (80%) of 14-1 as a white crystals, m.p. 104–106° C. ^{1}H NMR ($CDCl_3$, TMS) δ: 0.91 and 0.93 (total 6H, both s, 3,5-CH_{3eq}); 1.08 (2H, m, 2,6-CH_{eq}); 1.13 and 1.15 (total 6H, both s, 3,5-CH_{3ax}); 1.25 (2H, m, 4-CH_2); 1.32 and 1.38 (total 3H, both s, 1-CH_3); 1.70 and 2.12 (total 2H, both d, 14.7 Hz, 2,6-CH_{ax}); 5.30 and 5.60 (total 1H, both br s, NH); 8.05 and 8.30 ppm (total 1H, both d, 2.0 and 12.7 Hz, resp., HCO).

Preparation of N-acetyl-1,3,3,5,5-pentamethylcyclohexanamine (14-2).

To a vigorously stirred solution of 1,3,3,5,5-pentamethylcyclohexanol (3-13) (3.0 g, 17.65 mmol) in acetonitrile (20 ml) fuming HNO_3 (6 ml) was added dropwise, keeping temperature below 45° C. The resulting mixture was stirred at ~50° C. for 6 h, then it was cooled, poured into water (30 ml) and neutralised with aqueous NH_3. Aqueous phase was extracted with ether (3*30 ml). The combined ether phases were washed with saline (30 ml), then dried over $MgSO_4$, filtered and evaporated. The crude product was crystallised from cold acetonitrile to give 2.23 g (60%) of 14-2 as a white crystals, m.p. 110° C. ^{1}H NMR ($CDCl_3$, TMS) δ: 0.90 and 1.12 (total 12H, both s, 3,5-CH_3); 1.33 (3H, s, 1-CH_3); 1.88 (3H, s, CH_3C=O); 0.75–2.25 (6H, m, ring protons) and 5.3 ppm (1H, br s, NH).

Preparation of N-methoxycarbonyl-N,1,3,3,5-hexamethylcyclohexanamine (15).

Methyl chloroformate (0.97 g, 0.8 ml, 10.3 mmol) was added in one portion to a suspension of N,1,3,3,5,5-hexamethylcyclohexanamine hydrochloride (5-20) (1.13 g, 5.13 mmol) and Na_2CO_3 (1.63 g, 15.4 mmol) in THF (30 ml). The resulting mixture was stirred at room temperature for 6 h, and then it was diluted with water (50 ml) and extracted with ether (3*30 ml). The combined organic phases were washed with 10% K_2SO_4, saline, dried over $MgSO_4$, filtered and evaporated. The crude product was purified by flash chromatography, eluting with hexane—ethyl acetate mixture (6:1) to give 0.90 g (78%) of (15) as an oil. ^{1}H NMR ($CDCl_3$, TMS) δ: 0.93 and 1.07 (total 12H, both s, 3,5-CH_3); 1.23 (3H, s, 1-CH_3); 1.0–1.4 (4H, m, 4-CH_2 and 2,6-CH_{eq}); 2.56 (2H, d, J=14 Hz, 2,6-CH_{ax}); 2.87 (3H, s, CH_3N) and 3.64 ppm (6H, s, CH_3O).

Preparation of ethyl (3,3,5,5-tetramethylcyclohexylidene) cyanoacetate (16).

The mixture of 3,3,5,5-tetramethylcyclohexanone (2-13) (2.64 g, 17 mmol), ethyl cyanoacetate (1.93, 17 mmol), acetic acid (0.2 ml) and ammonium acetate (0.2 g) in benzene (6.4 ml) was refluxed with a Dean-Stark aparatus for 10 h. To this benzene (30 ml) and saline (30 ml) was added, organic layer separated, dried over Na_2SO_4, filtered and evaporated. The crude product was purified by flash chromatography, eluting with hexane to give 2.0 g (50%) of (16) as an oil. ^{1}H NMR ($CDCl_3$, TMS) δ: 1.01 (6H, s, 3,5-CH_{3eq}); 1.05 (6H, s, 3,5-CH_{3ax}); 1.34 (3H, t, J=7 Hz, ethyl-CH_3); 1.42 (2H, s, 4-CH_2); 2.46 and 2.79 (total 4H, both s, 2,6-CH_2) and 4.29 ppm (2H, q, J=7 Hz, CH_2O).

Preparation of ethyl (1,3,3,5,5-pentamethylcyclohexyl) cyanoacetate (17).

Anhydrous copper (I) chloride (0.8 g, 8 mmol) was added to a cooled solution of alkylmagnesium iodide (prepared from magnesium (0.46 g, 19.2 mmol) and iodomethane (2.84 g, 20 mmol)) in ether (12 ml). The mixture was stirred in an inert atmosphere for 5 min and a solution of ethyl (3,3,5,5-tetramethylcyclohexylidene)cyanoacetate (16) (2 g, 8 mmol) in ether (10 ml), was added dropwise keeping the temperature below −15° C. After the addition of ketone was completed, the reaction mixture was stirred for 3 h and carefully neutralised with saturated aqueous NH_4Cl solution. Traditional workup for Grignard reactions gave crude material which was separated on a silica gel column, eluting with a petroleum ether—ethyl acetate mixture (20:1) to give 1.0 g (47%) of 17 as an oil. ^{1}H NMR ($CDCl_3$, TMS) δ: 0.98 (9H, s, 3,5-CH_{3eq} and 1-CH_3); 1.06 (6H, s, 3,5-CH_{3ax}); 1.31 (3H, t, J=7 Hz, ethyl-CH_3); 1.2–1.5 (6H, m, ring protons); 3.41 (1H, s, α-CH) and 4.25 ppm (2H, q, J=7 Hz, CH_2O).

Preparation of 1-cyanomethyl-1,3,3,5,5-pentamethylcyclohexane (18).

The mixture of ethyl (1,3,3,5,5-pentamethylcyclohexyl) cyanoacetate (17) (1 g, 3.7 mmol), LiCl (0.05 g) and water (0.15 ml) in DMSO (2.5 ml) was heated at 150–160° C. for 4 h. Solution was poured into water (70 ml) and extracted with ether (4*20 ml). Ether was washed with saline (2*50 ml), dried over Na_2SO_4, filtered and evaporated. Crude product was purified on silica gel column, eluting with a petroleum ether—ethyl acetate mixture (20:1) to give 0.66 g (94%) of 18 as an oil. ^{1}H NMR ($CDCl_3$, TMS) δ: 0.98 (9H, s, 3,5-CH_{3eq} and 1-CH_3); 1.02 (6H, s, 3,5-CH_{3ax}); 1.21 (3H, s, ring protons); 1.31 (3H, s, ring protons) and 2.31 ppm (2H, s, CH_2CN). IR (neat) $\nu_{C\equiv N}$=2242 cm^{-1}.

General procedure for preparation of alkylcyclohexanamine hydrochlorides 5-1–5-25.

A solution of 4, 10 or 13–15, 18 in ether was added dropwise to a stirred suspension of lithium aluminum hydride (4 equivalents) in ether, which was cooled in an ice bath. The reaction mixture was stirred at room temperature in the case of 4, 10, 13 or refluxed in the case of 14, 15, 18 till complete conversion of starting material (TLC control). Residual lithium aluminum hydride was destroyed with water, the aqueous layer separated and twice extracted with ether. The combined ether phases were washed with saline.

dried over NaOH, filtered and evaporated. The amine obtained was treated with HCl without characterization. The amine hydrochloride was prepared either by passing of HCl gas through the amine solution in hexane or by addition of a 1 N HCl solution in ether to the amine solution. In both cases the solvent was removed after HCl addition, the residue treated with hexane or acetonitrile and the crystalline product filtered off to give 5-1–5-25 with excellent purity.

The physical properties and yields of compounds 5-1–5-25 are given in Table 4.

^{1}H NMR spectral data of compounds 5-1–5-25 are given in Table 5.

Additional 1-aminoalkylcyclohexanes and their hydrochlorides are prepared in the same or a similar manner. The hydrochlorides can be converted to the free base or other acid addition salts as disclosed under "ACID ADDITION SALTS".

Preparation of 3,3,5,5-tetramethylcyclohexylmethylamine hydrochloride (5-26).

A solution of 1-nitromethyl-3,3,5,5-tetramethylcyclohexene (6) (1.1 g, 5.63 mmol) in a mixture of ethanol (140 ml) and chloroform (2.8 ml) was hydrogenated over 10% Pd/C (280 mg) at 5 atm for 20 h, filtered and evaporated. The crude product was treated with ether, filtered and washed with ether to give 0.57 g (50%) of amine 5-26.

The physical properties and yield of compound 5-26 are given in Table 4.

^{1}H NMR spectral data of compound 5-26 are given in Table 5.

Amine 5-27 was prepared according to the known procedure [16].

Amine 5-28 [17] was prepared according to the general procedure from corresponding azide [18]. All physical properties were in good agreement with data described [17].

The purity of all compounds prepared was checked by GC (MN-OV-1, 25 m*0.53 m, d$_f$=1.0 μm, 50–270° C. (10° C./min)).

ACID ADDITION SALTS

As acids suitable for the formation of acid addition salts according to conventional procedure, there may be mentioned from the mineral series the following acids: *hydrochloric, hydrobromic, methanesulfonic, isothionic,* sulfuric, phosphoric, and sulfamic acids and, from the organic series: acetic, propionic, maleic, fumaric, tartaric, citric, oxalic, and benzoic acids, to name a few. Preferred acids are hydrochloric, citric, and maleic. Other pharmaceutically-acceptable acid addition salts may be prepared, if desired, and one acid addition salt may be converted into another by neutralizing one salt, for example, the hydrochloride, resulting in the free base, and then reacidifying with a different selected mineral or organic acid, to prepare another pharmaceutically-acceptable acid addition salt, as is conventional in the art.

TABLE 1

Cyclohexanones 2

Compd.	R^1	R^2	R^3	R^4	Yield (%)	^{1}H - NMR (CDCl$_3$, TMS) δ ppm
2-10	Me		Me	Pr	81.5	0.86 (3H, t, 6 Hz); 0.98 (3H, s); 1.01 (3H, d, 5 Hz); 1.05–1.35 (4H, m); 1.55–2.05 (4H, m); 2.11 (2H, s); 2.34 (1H, m)
2-11	Me	Me		Et	54	0.88 (3H, s); 0.90 (3H, t, 7 Hz); 1.06 (3H, s); 1.15–1.45 (2H, m); 2.13 (2H, s); 1.45–2.45 (5H, m)
2-12	Me	Me		Pr	74	0.87 (6H, m); 1.15 (3H, s); 1.15–1.45 (4H, m); 2.13 (2H, s); 1.45–2.45 (5H, m)
2-16	Me	Me	Et	Et	83.5	0.78 (6H, t, 7 Hz); 1.04 (6H, s); 1.37 (2H, q, 7 Hz); 1.52 (2H, s); 2.16 (4H, s)
2-17	Me	Me	Pr	Pr	79	0.87 (6H, m), 1.03 (6H, s); 1.25 (8H, m); 1.53 (2H, s); 2.16 (4H, s)

TABLE 2

1-Alkylcyclohexanols 3

Compd.	R^1	R^2	R^3	R^4	R^5	Yield (%)	^{1}H - NMR (CDCl$_3$, TMS) δ ppm
3-2a				Et	Me		0.84 (3H, t, 7 Hz); 1.17 (3H, s);1.0–1.85 (12H, m)
3-2b			Et		Me	93	0.87 (3H, t, 7 Hz); 1.21 (3H, s);1.0–1.85 (12H, m)
3-3a				Pr	Me		0.86 (3H, t, 7 Hz); 1.18 (3H, s);1.0–1.9 (14H, m)
3-3b			Pr		Me	93	0.86 (3H, t, 7 Hz); 1.19 (3H, s);1.0–1.85 (14H, m)
3-6a			Me	Pr	Me		0.83 (3H, s); 0.86 (3H, m); 1.19 (3H, s);1.0–1.85 (13H, m)
3-6b			Pr	Me	Me	88	0.86 (3H, t, 6.5 Hz); 1.04 (3H, s); 1.17 (3H, s); 0.95–1.95 (13H, m)
3-9	Me		Et	Me	Me	94	0.80 (3H, s); 0.81 (3H, t, 7 Hz); 0.86 (3H, d, 6.5 Hz); 1.17 (3H, s); 0.9–2.0 (10H, m)
3-10	Me		Pr	Me	Me	88	0.81 (6H, m); 0.86 (3H, d, 6.5 Hz); 1.17 (3H, s); 0.9–2.0 (12H, m)
3-11	Me	Me		Et	Me	84	0.87 (6H, m); 1.08 (3H, s); 1.18 (3H, s); 0.95–1.95 (10H, m)
3-12	Me	Me		Pr	Me	88	0.88 (6H, m); 1.09 (3H, s); 1.18 (3H, s); 0.9–1.95 (12H, m)
3-15	Me	Me	Me	Me	Pr	85	0.89 (9H, m); 1.21 (6H, s); 0.95–1.7 (11H, m)
3-16	Me	Me	Me (Et)	Et (Me)	Me	89	0.81 (3H, t, 7 Hz); 0.89, 1.17 and 1.21 (total 12H, all s); 0.9–1.35 (5H, m); 1.35–2.0 (4H, m)
3-17	Me	Me	Me (Pr)	Pr (Me)	Me	88	0.84(3H, m); 0.88 and 1.19 (total 12H, both s); 0.9–1.35 (7H, m); 1.35–2.0 (4H, m)
3-18	Me	Me	Et	Et	Me	87	0.78 (6H, t, 7 Hz); 0.89 (3H, s); 1.19 (6H, s); 0.95–1.3 (7H, m) ; 1.3–2.05 (4H, m)
3-19	Me	Me	Pr	Pr	Me	90	0.86 (6H, t, 6.5); 0.88 (3H, s); 1.18 (6H, s); 0.9–1.3 (11H, m); 1.3–2.05 (4H, m)

TABLE 3

1-Alkyl-1-azadodecylhexanes 4

Compound	R^1	R^2	R^2	R^4	R^5	Yield (%)	^1H - NMR ($CDCl_3$, TMS) δ ppm
4-1a				Me	Me	31	0.89 (3H, d, 6.5 Hz); 1.31 (3H, s); 0.95–2.0 (9H, m)
4-1b			Me		Me	6	0.92 (3H, d, 6.5 Hz); 1.28 (3H, s); 1.0–2.0 (9H, m)
4-2a				Et	Me	26	0.88 (3H, t, 7 Hz); 1.29 (3H, s); 0.95–2.0 (11H, m)
4-2b			Et		Me	4	0.88 (3H, t, 6.5 Hz); 1.27 (3H, s); 1.0–2.0 (11H, m)
4-3a				Pr	Me	24	0.88 (3H, t, 6.5 Hz); 1.29 (3H, s); 1.0–2.0 (13H, m)
4-3b			Pr		Me	11	0.88 (3H, t, 6.5 Hz); 1.27 (3H, s); 1.0–2.0 (13H, m)
4-4			Me	Me	Me	65	0.90 (3H, s); 1.08 (3H, s); 1.27 (3H, s); 1.0–1.95 (8H, m)
4-5			Me (Et)	Et (Me)	Me	60	0.82 and 1.04 (total 3H, s); 0.82 (3H, t, 7 Hz); 1.28 and 1.29 (total 3H, s); 0.9–2.0 (10H, m)
4-6			Me (Pr)	Pr (Me)	Me	66	0.85 and 1.07 (total 3H, s); 0.87 and 0.90 (total 3H, t, 6.5 Hz); 1.29 (3H, s); 1.0–1.95 (12H, m)
4-7	Me (H)	H (Me)	H (Me)	Me (H)	Me	31	0.87 (6H, d, 6 Hz); 1.27 and 1.29 (total 3H, s); 0.95–2.15 (8H, m)
4-8a	Me		Me	Me	Me	42	0.86 (3H, d, 6 Hz); 0.89 (3H, s); 1.09 (3H, s); 1.27 (3H, s); 0.95–1.9 (7H, m)
4-8b		Me	Me	Me	Me	12	0.92 (3H, d, 6 Hz); 0.94 (3H, s); 0.97 (3H, s); 1.36 (3H, s); 0.95–2.0 (7H, m)
4-9a	Me		Et	Me	Me	47	0.81 (6H, s and m); 0.86 (3H, d, 6 Hz); 1.27 (3H, s); 0.95–1.95 (9H, m)
4-9b		Me	Me	Et	Me	12	0.81 (3H, t, 7 Hz); 0.87 (3H, s); 0.91 (3H, d, 6 Hz); 1.34 (3H, s); 0.95–(9H, m)
4-10a	Me		Pr	Me	Me	44	0.81 (3H, s); 0.84 (3H, d, 6 Hz); 0.87 (3H, m); 1.27 (3H, s); 1.0–2.0 (11H, m)
4-10b		Me	Me	Pr	Me	9	0.88 (6H, s and m); 0.91 (3H, d, 6 Hz); 1.34 (3H, s); 1.0–1.95 (11H, m)
4-11a	Me	Me		Et	Me	45	0.91 (3H, t, 7 Hz); 0.92 (3H, s); 1.12 (3H, s); 1.31 (3H, s); 1.0 –1.9 (9H, m)
4-11b	Me	Me	Et		Me	12	0.92 (3H, t, 7 Hz); 0.97 and 0.99 (total 6H, s); 1.37 (3H, s); 1.0–1.9 (9H, m)
4-12a	Me	Me		Pr	Me	54	0.90(6H, s and m); 1.10 (3H, s); 1.28 (3H, s);0.95–1.9 (11H, m)
4-12b	Me	Me	Pr		Me	7	0.89 (3H, t, 7 Hz); 0.95 (3H, s); 0.98 (3H, s); 1.37 (3H, s); 1.0–1.9 (11H, m)
4-13	Me	Me	Me	Me	Me	67	0.89 (6H, s); 1.18 (6H, s); 1.29 (3H, s); 0.95–1.9 (6H, m)
4-14	Me	Me	Me	Me	Et	39	0.89 (6H,s); ().96 (3H, t, 7 Hz); 1.19 (6H, s); 1.0–1.9 (8H, m)
4-15	Me	Me	Me	Me	Pr	65	0.89 (6H, s); 0.93 (3H, m); 1.18 (6H, s); 1.0–1.8 (10H, m)
4-16	Me	Me	Me (Et)	Et (Me)	Me	77	0.82 (3H, m); 0.89, 1.14 and 1.18 (total 9H, s); 1.26 and 1.29 (total 3H, s); 0.95–1.9 (8H, m)
4-17	Me	Me	Me (Pr)	Pr (Me)	Me	71	0.86; 0.88 (total 3H, t, 6.5 Hz); 0.90, 1.17; 1.19 (total 9H, s); 1.28; 1.32 (total 3H); 0.95–1.9 (10H, m)
4-18	Me	Me	Et	Et	Me	66	0.78 (6H, t, 7 Hz); 0.90 (3H, s); 1.18 (3H, s); 1.31 (3H, s); 0.95–1.95 (10H, m)
4-19	Me	Me	Pr	Pr	Me	61	0.89 (9H, s and m); 1.17 (3H, s); 1.27 (3H, s); 0.95–1.95 (14H, m)

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TABLE 4

Amino-cyclohexane derivatives 5

Mr:				Elemental analysis							
				Calculated (%)			Found (%)			m.p.	Yield
2/	Comp	Formula	M.W.	C	H	N	C	H	N	(° C.)	(%)
625	5-1a	$C_9H_{17}N.HCl$	163.72	58.7	10.5	8.6	58.7	10.5	8.6	>250	63
631	5-1b	$C_9H_{17}N.HCl$	163.72	58.7	10.5	8.6	58.7	10.5	8.6	200–202	48
629	5-2a	$C_{10}H_{19}N.HCl$	177.75	60.8	10.8	7.9	60.8	10.8	7.9	>250	66
630	5-2b	$C_{10}H_{19}N.HCl$	177.75	60.8	10.8	7.9	60.8	10.8	7.9	179–181	43
627	5-3a	$C_{10}H_{21}N.HCl$	191.78	62.6	11.1	7.3	62.6	11.1	7.3	>250	80
628	5-3b	$C_{10}H_{21}N.HCl$	191.78	62.6	11.1	7.3	62.6	11.1	7.3	181–182	81
621	5-4	$C_{10}H_{19}N.HCl$	177.75	60.8	10.8	7.9	60.8	10.8	7.9	230–231	73
620	5-5	$C_{10}H_{21}N.HCl$	191.78	62.6	11.1	7.3	62.6	11.1	7.3	168–170	71
617	5-6	$C_{11}H_{23}N.HCl$	205.81	64.2	11.3	6.8	64.2	11.3	6.8	106–108	68
616	5-7	$C_{10}H_{19}N.HCl$	177.75	60.8	10.8	7.9	60.8	10.8	7.9	280–282	50
607	5-8a	$C_{10}H_{21}N.HCl$	191.78	62.6	11.1	7.3	62.6	11.1	7.3	>240	74
622	5-9a	$C_{11}H_{23}N.HCl$	205.81	64.2	11.3	6.8	64.2	11.3	6.8	250–253	68
624	5-9b	$C_{11}H_{23}N.HCl$	205.81	64.2	11.3	6.8	64.2	11.3	6.8	228–231	60
618	5-10a	$C_{12}H_{25}N.HCl$	219.84	65.6	11.9	6.4	65.6	11.5	6.4	167–168	57
619	5-10b	$C_{12}H_{25}N.HCl$	219.84	65.6	11.9	6.4	65.6	11.5	6.4	237–238	36
633	5-11a	$C_{11}H_{23}N.HCl$	205.81	64.2	11.3	6.8	64.2	11.3	6.8	255–257	69
632	5-11b	$C_{11}H_{23}N.HCl$	205.81	64.2	11.3	6.8	64.2	11.3	6.8	216–218	44
635	5-12a	$C_{12}H_{25}N.HCl$	219.84	65.6	11.9	6.4	65.6	11.5	6.4	218–221	83
634	5-12b	$C_{12}H_{25}N.HCl$	219.84	65.6	11.9	6.4	65.6	11.5	6.4	200–203	44

TABLE 4-continued

Amino-cyclohexane derivatives 5

Mrz				Elemental analysis						m.p.	Yield
				Calculated (%)			Found (%)				
y	Comp	Formula	M.W.	C	H	N	C	H	N	(° C.)	(%)
579	5-13	$C_{13}H_{23}N.HCl$	205.81	64.2	11.5	6.8	64.2	11.3	6.8	235–237	82
600	5-14	$C_{17}H_{29}N.HCl.H_2O$	237.86	60.6	10.6	5.9	60.6	10.6	5.9	215–218	74
601	5-15	$C_{13}H_{27}N.HCl$	233.87	66.8	11.7	6.0	66.8	11.7	6.0	>280	88
615	5-16	$C_{12}H_{25}N.HCl$	219.84	65.6	11.9	6.4	65.6	11.5	6.4	162–163	65
614	5-17	$C_{13}H_{25}N.HCl.0.5H2$	242.84	64.3	12.0	5.8	63.8	12.0	5.6	106–107	54
623	5-18	$C_{13}H_{27}N.HCl.H_2O$	251.89	62.0	10.8	5.6	62.0	10.8	5.6	99–102	78
626	5-19	$C_{15}H_{31}N.HCl$	261.93	68.8	12.0	5.3	68.8	12.0	5.3	167–169	72
640	5-20	$C_{12}H_{25}N.HCl$	219.84	65.6	11.9	6.4	65.6	11.7	6.3	249–251	86
639	5-21	$C_{13}H_{27}N.HCl$	233.82	66.8	12.1	6.0	66.6	12.3	5.9	257–259	82
642	5-22	$C_{13}H_{27}N.HCl.H_2O$	251.82	62.0	12.0	5.6	62.0	12.0	5.5	>210	98
645	5-23	$C_{14}H_{29}N.HCl$	247.85	67.8	12.2	5.7	67.6	12.3	5.6	205–207	89
644	5-24	$C_{12}H_{25}N.HCl$	219.84	65.6	11.9	6.4	65.4	11.9	6.2	>250	83
662	5-25	$C_{13}H_{27}N.HCl.0.5H_2O$	242.84	64.3	12.0	5.8	64.9	11.9	5.7	>250	64
580	5-26	$C_{11}H_{23}N.HCl$	205.81	64.2	11.3	6.8	64.1	11.4	6.9	>230	50
557	5-27	$C_{10}H_{21}N.HCl$	191.75	62.6	11.6	7.3	62.3	11.6	7.2	>250 (dec.)	70
641	5-28	C7H15N.HCl	149.7	56.2	10.8	9.4	55.9	11.0	9.2	283–285	69

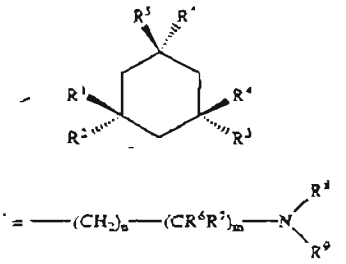
TABLE 5

Spectral data of Amino-cyclohexane derivatives 5

Compd.	^1H - NMR (CDCl, TMS) δ ppm
5-1a	0.69 (3H, d, 6 Hz); 0.9–1.4 (3H, m); 1.44 (3H, s); 1.5–2.3 (6H, m); 8.3 (3H, br s)
5-1b	0.90 (3H, d, 5 Hz); 1.46 (3H, s); 1.0–2.3 (9H, m); 8.3 (3H, br s)
5-2a	0.87 (3H, t, 7 Hz); 1.45 (3H, s); 1.0–2.3 (11H, m); 8.35 (3H, br s)
5-2b	0.87 (3H, t, 7 Hz); 1.46 (3H, s); 1.0–2.2 (11H, m); 8.3 (3H, br s)
5-3a	0.86 (3H, t, 6.5 Hz); 0.95–1.4 (1H, m); 1.45 (3H, s); 1.5–2.2 (6H, m); 8.3 (3H, br s)
5-3b	0.85 (3H, t, 1 Hz); 1.47 (3H, s); 0.95–2.2 (13H, m); 8.3 (3H, br s)
5-4	0.96 (3H, s), 1.05 (3H, s); 1.50 (3H, s); 1.1–1.95 (8H, m); 8.25 (3H, br s)
5-5	0.82 (3H, t, 1 Hz); 0.90 and 1.04 (total 3H, both s); 1.48 and 1.50 (total 3H, both s); 1.1–2.0 (10H, m); 8.25 (3H, br s)
5-6	0.86 (3H, m); 0.94 and 1.07 (total 3H, both s); 1.49 and 1.52 (total 3H, both s); 1.1–2.0 (12H, m); 8.25 (3H, br s)
5-7	0.90 (6H, d, 6 Hz); 1.44 and 1.50 (total 3H, both s); 0.95–2.4 (8H, m); 8.25 (3H, br s)
5-8a	0.90 and 0.91 (total 6H, d, s); 1.23 (3H, s); 1.44 (3H, s); 0.95–2.3 (7H, m); 8.2 (3H, br s)
5-9a	0.83 (s) and 0.81 (m, total 9H); 1.41 (3H, s); 1.0–2.2 (9H, m); 8.15 (3H, br s)
5-9b	0.7–1.0 (m) and 0.89 (s, total 9H); 1.55 (3H, s); 1.05–2.2 (9H, m); (3H, br s)
5-10a	0.1–0.95 (m) and 0.88 (s, total 9H); 1.51 (3H, s); 0.95–2.3 (11H, m); 8.2 (3H, br s)
5-10b	0.7–1.0 (m) and 0.90 (s, total 9H); 1.54 (3H, s); 1.05–2.1 (11H, m); 82 (3H, br s)
5-11a	0.8 1.0 (m) and 0.91 (s, total 6); 1.22 (3H, s), 1.44 (3H, s); 1.0–2.3 (9H, m); 8.2 (3H, br s)
5-11b	0.88 (m) and 0.96 (s, total 9H); 1.50 (3H, s); 1.0–2.15 (9H, m); 8.2 (3H, br s)
5-12a	0.91 (6H, m); 1.22 (3H, s); 1.45 (3H, s); 1.0–2.3 (11H, m); 8.2 (3H, br s)
5-12b	0.89 (m); 0.97 (s, total 9H); 1.54 (3H, s); 1.0–2.2 (11H, m); 8.2 (3H, br s)
5-13	1.02 and 1.07 (total 12H, s); 1.26 (2H, m); 1.62 (3H, s); 1.71 (4H, m)
5-14	1.03 and 1.07 (total 12H, s); 1.09 (3H, t, 7 Hz); 1.29 (2H, s); 1.59 and 1.81 (total 4H, d, 14 Hz); 1.96 (2H, q, 7 Hz); 8.15 (3H, br s)
5-15	0.93 (3H, t, 1 Hz); 1.01 and 1.04 (total 12H, s); 1.29 (2H, s); 1.35–2.0 (4H, m); 1.70 (4H, m); 8.2 (3H, br s)
5-16	0.83 (3H, m); 1.00, 1.02 and 1.07 (total 9H, s); 1.2–1.5 (4H, m); 1.59 and 1.63 (total 3H, both s); 1.70 (4H, m), 8.25 (3H, br s)
5-17	0.87 (3H, m); 1.0–1.1 (9H, m); 1.1–1.4 (6H, m); 1.60 and 1.64 (total 3H, both s); 1.70 (4H, m); 8.25 (3H, br s)
5-18	0 78 (6H, t, 7 Hz); 1.04 (6H, s); 1.21 (2H, m); 1.40 (4H, m); 1.59 (3H, s); 1.6–1.8 (4H, m); 8.25 (3H, br s)
5-19	0.87 (6H, m); 1.04 (6H, s); 1.1–1.5 (10H, m); 1.60 (3H, s); 1.5–1.95 (4H, m); 8.2 (3H, br s)
5-20	1.00 and 1.11 (total 12H, s); 1.29 (2H, m); 1.57 (3H, s); 1.72 (4H, dd, 14 Hz); 2.56 (3H, t, 6 Hz); 9.2 ppm (2H, br s)
5-21	0 98 and 1.11 (total 12H, s); 1.29 (2H, m); 1.58 (3H, t, 7 Hz); 1.61 (3H, s); 1.82 (4H, m); 3.0 (2H, m); 9.1 ppm (2H, br s)
5-22	1.03 and 1.12 (total 12H, s); 1.32 (2H, m); 1.45 (3H, s); 1.64 and 1.97 (total 4H, d, 14 Hz); 2.69 (6H, d, 5 Hz)
5-23	0.85 (6H, s); 1.02 (6H, s); 0.6–1.95 (7H, m); 1.46 (6H, s); 1.60 (2H, d, 5 Hz); 0.35 (3H, br s)
5-24	0.61 (6H, s); 0.98 (6H, s); 0.6–1.85 (9H, m); 3.02 (2H, m); 8.30 (3H, br s)
5-25	0.96 (6H, s), 1.02 (6H, s); 1.01 (3H, s); 1.18 (6H, s); 1.73 (2H, m); 3.03 (2H, m); 8.29 (3H, br s)
5-26	0 97 (12H, br s); 1.0–2.2 (7H, m); 2.30 (2H, m); 8.35 ppm (3H, br s).
5-27	0.97 (6H, s); 1.04 (6H, s); 1.12 (1H, d, 13.7 Hz); 1.2–1.4 (5H, m); 1.92 (2H, d, 12.3 Hz); 3.41 (1H, m); 8.30 (3H, br s)
5-28	1.47 (3H, s) 1.2–2.2 (10H, m); 8.3 (3H, br s)

TABLE 6

Basic Structure of the amino- and aminoalkylcyclohexanes.



$R^* = -(CH_2)_n-(CR^6R^7)_m-N(R^8)(R^9)$

n + m = 0, 1, 2
R^1–R^9 = lower alkyl

Mfz J/	Compd	R^1	R^2	R^3	R^4	R^5	R^*
625	5-1a	H	H	H	Me	Me	NH_2
631	5-1b	H	H	Me	H	Me	NH_2
629	5-2a	H	H	H	Et	Me	NH_2
630	5-2b	H	H	Et	H	Me	NH_2
627	5-3a	H	H	H	Pr	Me	NH_2
628	5-3b	H	H	Pr	H	Me	NH_2
621	5-4	H	H	Me	Me	Me	NH_2
620	5-5	H	H	Me (Et)	Et (Me)	Me	NH_2
617	5-6	H	H	Me (Pr)	Pr (Me)	Me	NH_2
616	5-7	Me (H)	H (Me)	H (Me)	Me (H)	Me	NH_2
643	5-8a	Me	Me	Me	H	Me	NH_2
607	5-8a	Me	Me	H	Me	Me	NH_2
622	5-9a	Me	H	Et	Me	Me	NH_2
624	5-9b	H	Me	Me	Et	Me	NH_2
618	5-10a	Me	H	Pr	Me	Me	NH_2
619	5-10b	H	Me	Me	Pr	Me	NH_2
633	5-11a	Me	Me	H	Et	Me	NH_2
632	5-11b	Me	Me	Et	H	Me	NH_2
635	5-12a	Me	Me	H	Pr	Me	NH_2
634	5-12b	Me	Me	Pr	H	Me	NH_2
579	5-13	Me	Me	Me	Me	Me	NH_2
600	5-14	Me	Me	Me	Me	Et	NH_2
601	5-15	Me	Me	Me	Me	Pr	NH_2
615	5-16	Me	Me	Me (Et)	Et (Me)	Me	NH_2
614	5-17	Me	Me	Me (Pr)	Pr (Me)	Me	NH_2
623	5-18	Me	Me	Et	Et	Me	NH_2
626	5-19	Me	Me	Pr	Pr	Me	NH_2
640	5-20	Me	Me	Me	Me	Me	NHMe
639	5-21	Me	Me	Me	Me	Me	NHEt
642	5-22	Me	Me	Me	Me	Me	$N(Me)_2$
645	5-23	Me	Me	Me	Me	H	$CH_2CMe_2NH_2$
644	5-24	Me	Me	Me	Me	H	$CH_2CH_2NH_2$
662	5-25	Me	Me	Me	Me	Me	$CH_2CH_2NH_2$
580	5-26	Me	Me	Me	Me	H	CH_2NH_2
557	5-27	Me	Me	Me	Me	H	NH_2
641	5-28	H	H	H	H	Me	NH_2
705	infra	Me	Me	Me	Me	Me	N-pyrrolidine

PHARMACEUTICAL COMPOSITIONS

The active ingredients of the invention, together with one or more conventional adjuvants, carriers, or diluents, may be placed into the form of pharmaceutical compositions and unit dosages thereof, and in such form may be employed as solids, such as coated or uncoated tablets or filled capsules, or liquids, such as solutions, suspensions, emulsions, elixirs, or capsules filled with the same, all for oral use; in the form of suppositories or capsules for rectal administration or in the form of sterile injectable solutions for parenteral (including intravenous or subcutaneous) use. Such pharmaceutical compositions and unit dosage forms thereof may comprise conventional or new ingredients in conventional or special proportions, with or without additional active compounds or principles, and such unit dosage forms may contain any suitable effective amount of the active ingredient commensurate with the intended daily dosage range to be employed. Tablets containing twenty (20) to one hundred (100) milligrams of active ingredient or, more broadly, ten (10) to two hundred fifty (250) milligrams per tablet, are accordingly suitable representative unit dosage forms.

METHOD OF TREATING

Due to their high degree of activity and their low toxicity, together presenting a most favorable therapeutic index, the active principles of the invention may be administered to a subject, e.g., a living animal (including a human) body, in need thereof, for the treatment, alleviation, or amelioration, palliation, or elimination of an indication or condition which is susceptible thereto, or representatively of an indication or condition set forth elsewhere in this application, preferably concurrently, simultaneously, or together with one or more pharmaceuti- cally-acceptable excipients, carriers, or diluents, especially and preferably in the form of a pharmaceutical composition thereof, whether by oral, rectal, or parental (including intravenous and subcutaneous) or in some cases even topical route, in an effective amount. Suitable dosage ranges are 1–1000 milligrams daily, preferably 10–500 milligrams daily, and especially 50–500 milligrams daily, depending as usual upon the exact mode of administration, form in which administered, the indication toward which the administration is directed, the subject involved and the body weight of the subject involved, and the preference and experience of the physician or veterinarian in charge.

EXAMPLES OF REPRESENTATIVE PHARMACEUTICAL COMPOSITIONS

With the aid of commonly used solvents, auxiliary agents and carriers, the reaction products can be processed into tablets, coated tablets, capsules, drip solutions, suppositories, injection and infusion preparations, and the like and can be therapeutically applied by the oral, rectal, parenteral, and additional routes. Representative pharmaceutical compositions follow.

(a) Tablets suitable for oral administration which contain the active ingredient may be prepared by conventional tabletting techniques.

(b) For suppositories, any usual suppository base may be employed for incorporation thereinto by usual procedure of the active ingredient, such as a polyethyleneglycol which is a solid at normal room temperature but which melts at or about body temperature.

(c) For parental (including intravenous and subcutaneous) sterile solutions, the active ingredient together with conventional ingredients in usual amounts are employed, such as for example sodium chloride and double-distilled water q.s., according to conventional procedure, such as filtration, aseptic filling into ampoules or IV-drip bottles, and autoclaving for sterility.

Other suitable pharmaceutical compositions will be immediately apparent to one skilled in the art.

The following examples are againgiven by way of illustration only and are not to be construed as limiting.

EXAMPLE 1

Tablet Formulation A suitable formulation for a tablet containing 10 milligrams of active ingredient is as follows:

	Mg.
Active Ingredient	10
Lactose	63
Microcrystalline Cellulose	21
Talcum	4
Magnesium stearate	1
Colloidal silicon dioxide	1

EXAMPLE 2

Tablet Formulation

Another suitable formulation for a tablet containing 100 mg is as follows:

	Mg.
Active Ingredient	100
Potato starch	20
polyvinylpyrrolidone	10
Film coated and colored. The film coating material consists of:	
Lactose	100
Microcryst. Cellulose	80
Gelatin	10
Polyvinylpyrrolidone, crosslinked	10
Talcum	10
Magnesium stearate	2
Colloidal silicon dioxide	3
Color pigments	5

EXAMPLE 3

Capsule Formulation

A suitable formulation for a capsule containing 50 milligrams of active ingredient is as follows:

	Mg
Active Ingredient	50
Corn starch	20
Dibasic calcium phosphate	50
Talcum	2
Colloidal silicon dioxide	2
filled in a gelatin capsule.	

EXAMPLE 4

Solution for Injection

A suitable formulation for an injectable solution containing one percent of active ingredient is as follows:

Active Ingredient	mg 12
Sodium chloride	mg 8
Sterile water to make	ml 1

EXAMPLE 5

Liquid Oral Formulation

A suitable formulation for 1 liter of a liquid mixture containing 2 milligrams of active ingredient in one milliliter of the mixture is as follows:

	G.
Active Ingredient	2
Saccharose	250
Glucose	300
Sorbitol	150
Orange flavor	10
Sunset yellow.	
Purified water to make a total of 1000 ml.	

EXAMPLE 6

Liquid Oral Formulation

Another suitable formulation for 1 liter of a liquid mixture containing 20 milligrams of active ingredient in one milliliter of the mixture is as follows:

	G.
Active Ingredient	20
Tragacanth	7
Glycerol	50
Saccharose	400
Methylparaben	0.5
Propylparaben	0.05
Black currant-flavor	10
Soluble Red color	0.02
Purified water to make a total of 1000 ml.	

EXAMPLE 7

Liquid Oral Formulation

Another suitable formulation for 1 liter of a liquid mixture containing 2 milligrams of active ingredient in one milliliter of the mixture is as follows:

	G.
Active Ingredient	2
Saccharose	400
Bitter orange peel tincture	20
Sweet orange peel tincture	15
Purified water to make a total of 1000 ml.	

EXAMPLE 8

Aerosol Formulation

180 g aerosol solution contain:

	G.
Active Ingredient	10
Oleic acid	5
Ethanol	81
Purified Water	9
Tetrafluoroethane	75

15 ml of the solution are filled into aluminum aerosol cans, capped with a dosing valve, purged with 3.0 bar.

EXAMPLE 9

TDS Formulation

100 g solution contain:

	G.
Active Ingredient	10.0
Ethanol	57.5
Propyleneglycol	7.5
Dimethylsulfoxide	5.0
Hydroxyethylcellulose	0.4
Purified water	19.6

1.8 ml of the solution are placed on a fleece covered by an adhesive backing foil. The system is closed by a protective liner which will be removed before use.

EXAMPLE 10

Nanoparticle Formulation

10 g of polybutylcyanoacrylate nanoparticles contain:

	G.
Active Ingredient	1.0
Poloxamer	0.1
Butylcyanoacrylate	8.75
Mannitol	0.1
Sodiumchloride	0.05

Polybutylcyanoacrylate nanoparticles are prepared by emulsion polymersiation in a water/0.1 N HCl/ethanol mixture as polymerisation medium. The nanoparticles in the suspension are finally lyophilized under vacuum.

PHARMACOLOGY—SUMMARY

The active principles of the present invention, and pharmaceutical compositions thereof and method of treating therewith, are characterized by unique advantageous and unpredictable properties, rendering the "subject matter as a whole", as claimed herein, unobvious. The compounds and pharmaceutical compositions thereof have exhibited, in standard accepted reliable test procedures, the following valuable properties and characteristics:

They are systemically-active, uncompetitive NMDA receptor antagonists with rapid blocking/unblocking kinetics and strong voltage dependency and are accordingly of utility in the treatment, elimination, palliation, alleviation, and amelioration of responsive conditions, by application or administration to the living animal host for the treatment of a wide range of CNS disorders which involve disturbances of glutamatergic transmission.

PHARMACOLOGY

In vitro

Receptor Binding Studies

Male Sprague-Dawley rats (200–250 g) were decapitated and their brains were removed rapidly. The cortex was dissected and homogenized in 20 volumes of ice-cold 0.32 M sucrose using a glass-Teflon homogenizer. The homogenate was centrifuged at 1000 ×g for 10 minutes. The pellet was discarded and the supernatant centrifuged at 20.000 ×g for 20 minutes. The resulting pellet was re-suspended in 20 volumes of distilled water and centrifuged for 20 minutes at 8000 ×g. Then the supernatant and the buffy coat were centrifuged three times (48.000 ×g for 20 minutes) in the presence of 50 mM Tris-HCl, pH 8.0. All centrifugation steps were carried out at 4° C. After resuspension in 5 volumes of 50 mM Tris-HCl, pH 8.0 the membrane suspension was frozen rapidly at −80° C. On the day of assay the membranes were thawed and washed four times by resuspension in 50 mM Tris-HCl, pH 8.0 and centrifugation at 48.000 ×g for 20 minutes. The final pellet was suspended in assay buffer. The amount of protein in the final membrane preparation was determined according to the method of Lowry with some modifications. The final protein concentration used for our studies was between 250–500 ug/mL.

Membranes were re-suspended and incubated in 50 mM Tris-HCl, pH 8.0. Incubations were started by adding [^{3}H]-(+)-MK-801 (23.9 Ci/mmol, 5 nM) to vials with glycine (10 μM), glutamate (10 μM), and 0.1–0.25 mg protein (total volume 0.5 ml) and various concentrations of the agents tested (10 concentrations in duplicates). The incubations were continued at room temperature for 120 minutes, equilibrium always being achieved under the conditions used. Non-specific binding was defined by the addition of unlabeled MK-801 (10 μM). Incubations were terminated using a Millipore filter system. The samples were rinsed three times with 2.5 ml ice cold assay buffer over glass fiber filters obtained from Schleicher & Schuell under a constant vacuum. Filtration was performed as rapidly as possible. Following separation and rinse, the filters were placed into scintillation liquid (5 ml; Ultima Gold) and radio activity retained on the filters was determined with a conventional liquid scintillation counter (Hewlett Packard, Liquid Scintillation Analyser).

Patch Clamp

Hippocampi were obtained from rat embryos (E20 to E21) and were then transferred to calcium and magnesium free Hank's buffered salt solution (Gibco) on ice. Cells were mechanically dissociated in 0.05% DNAase/0.3% ovomucoid (Sigma) following an 8 minute pre-incubation with 0.66% trypsin/0.1% DNAase (Sigma). The dissociated cells were then centrifuged at 18 ×g for 10 minutes, re-suspended in minimum essential medium (Gibco) and plated at a density of 150.000 cells cm^{-2} onto poly-L-lysine (Sigma)-precoated plastic petri dishes (Falcon). The cells were nourished with $NaHCO_3$/HEPES-buffered minimum essential medium supplemented with 5% fetal calf serum and 5% horse serum (Gibco) and incubated at 37° C. with 5% CO_2 at 95% humidity. The medium was exchanged completely following inhibition of further glial mitosis with cytosine-β-D-arabinofuranoside (20 μM Sigma) after about 7 days in vitro. Thereafter the medium was exchanged partially twice weekly.

Patch clamp recordings were made from these neurones with polished glass electrodes (4–6 mΩ) in the whole cell mode at room temperature (20–22° C.) with the aid of an EPC-7 amplifier (List). Test substances were applied by switching channels of a custom-made fast superfusion system with a common outflow (10–20 ms exchange times). The contents of the intracellular solution were as follows (mM): CsCl (120), TEACl (20), EGTA (10), $MgCl_2$(1), $CaCl_2$-(0.2), glucose (10), ATP(2), cAMP (0.25); pH was adjusted to 7.3 with CsOH or HCl. The extracellular solutions had the following basic composition (mM): NaCl (140), KCl (3), $CaCl_2$ (0.2), glucose (10), HEPES (10), sucrose (4.5), tetrodotoxin (TTX $3*10^{-4}$). Glycine (1 μM) was present in all solutions: a concentration sufficient to cause around 80–85% activation of $glycine_B$ receptors. Only results from stable cells were accepted for inclusion in the final analysis, i.e., following recovery of responses to NMDA by at least 75% of their depression by the antagonists tested.

Excitotoxicity

Cortical neurones were obtained from cerebral cortices of 17/18 day old fetal rats (Wistar), in general following the dissociation procedure described by [23]. After short trypsinization and gentle trituration with fire-polished Pasteur pipettes, the cell suspension was washed by centrifugation. Cells were suspended in serum-free Neurobasal medium with B27 supplement (GIBCO) before plating onto poly-L-lysine (Sigma: 0.2 mg/ml, 20 h, 4° C.) and laminin (Sigma: 2 μg/ml, 1 h, 37° C.)-coated 96-well plates (Falcon, Primaria) at a density of 5×10^4 cells/well. Cortical neurones were maintained at 37° C. in humidified 10% CO_2/90% air. One day after plating, 5 μM cytosine-β-D-arabinofuranoside (Sigma) was added to each well for inhibition of glial cell proliferation. The medium was changed first after 4 days in vitro and then every 4 days by replacing ½ of the medium with astrocyte-conditioned medium. Cortical neurones between day 12 and 14 in culture were used for the experiments.

New-born rat astrocytes were isolated non-enzymatically according to the method of [24]. Briefly, both hemispheres were dissected from 2-day-old rats, passed through an 80 μm gauze, and triturated with Pasteur pipettes. Cell suspension was made in Dulbecco's modified essential medium (DMEM, Gibco) supplemented with 10% fetal calf serum (FCS, Hyclone), 2 mM glutamine (Gibco) and 50 μg/ml gentamycin and transferred into untreated, plastic culture flasks (Corning: 75 cm^3). Two days after plating the flasks were shaken for 10 minutes on a rotary platform (150 U/min) to remove microglial cells. The cultures were grown to confluency within 14 days, and the culture medium was changed twice weekly. Thereafter, the glial monolayers were extensively washed with serum-free Neurobasal medium (Gibco) to remove the serum. Flasks were then shaken several times to remove oligodendrocytes and neurones. To obtain conditioned medium from primary astrocytes, the cultures were incubated with fresh Neurobasal medium supplemented with B27 andglutamine. Every 2–3 days the conditioned medium was collected and replaced by fresh medium up to 4 times.

Exposure to EAA was performed in serum-free Neurobasal medium containing 100 μM glutamate and the drug to be tested. After 20 h of incubation, the cytotoxic effect was morphologically examined under a phase contrast microscope and biochemically quantified by measuring cell viability with the MTT test (Promega). This calorimetric assay measures the reduction of a tetrazolium component (MTT) into an insoluble formazan product by the mitochondria of living cells. After incubation of the cortical neurones with the dye solution for approximately 1–4 hours, a solubilization solution was added to lyse the cells and solubilize the colored product (incubation overnight at 37° C., 10% CO_2, 90% RH). These samples were then read using an Elisa plate reader (Thermomax, MWG Biotech) at a wavelength of 570 nm. The amount of color produced was directly proportional to the number of viable cells.

In vivo

Anticonvulsive activity

NMR female mice (18–28 g) housed 5 per cage were used for the maximal electroshock (MES) and motor impairment tests. All animals were kept with water and food ad libitum under a 12 hour light-dark cycle (light on at 6 a.m.) and at a controlled temperature (20±0.5° C.). All experiments were performed between 10 a.m. and 5 p.m. Tested agents were injected 30 min. i.p. before the induction of convulsions if not stated otherwise (see below). All compounds were dissolved in 0.9% saline.

The MES test was performed together with tests for myorelaxant action (traction reflex) and motor coordination (rotarod). For the traction reflex test mice were placed with their forepaws on a horizontal rod and were required to place all 4 paws on the wire within 10 seconds. To test ataxia (motor coordination) mice were placed on rotarod (5 rpm) and were required to remain on the rod for 1 minute. Only mice not achieving the criteria in all three repetitions of each test were considered to exhibit myorelaxation or ataxia respectively. These tests were followed by MES (100 Hz, 0.5 second shock duration, 50 mA shock intensity, 0.9 ms impulse duration, Ugo Basile) applied through corneal electrodes. The presence of tonic convulsions was scored (tonic extension of hind paws with minimum angle to the body of 90°). The aim was to obtain ED_{50}s for all parameters scored (anticonvulsive activity and motor side effects) with use of the Litchfield Wilcoxon test for quantal dose responses. Division of the ED_{50} for side effects (ataxia or myorelaxation) by the ED_{50} for antagonism of electroshock convulsions was used as a therapeutic index (TI).

Statistical Analysis

IC_{50}s in patch clamp, excitotoxicity, and binding studies were calculated according to the four parameter logistic equation using the Grafit computer program (Erithacus Software, England). Ki value for binding studies were then determined according to Cheng and Prusoff. Binding values presented are means±SEM of 3–5 determinations (each performed in duplicate). 4–7 doses of antagonists were tested in each of the in e vivo tests (5–8 animals per dose) to allow calculation of graded ED_{50}s according to probit analysis (Litchfield and Wilcoxon) with correction for 0% to 100% effects. ED_{50}s are presented with 95% confidence limits (CI). Pearson product moment correlation analysis (Sigma Stat, Jandel Scientific) was used to compare in vitro potencies and in vivo anticonvulsant activity.

RESULTS

Binding

All cyclohexanes displaced [^{3}H]-(+)-MK-801 binding to rat cortical membranes with IC_{50}s of between 4 and 150 μM whilst Ki values as assessed with the Cheng-Prussoff equation were 2 fold lower (see Table 7).

Patch Clamp

Steady-state inward current responses of cultured hippocampal neurones to NMDA (200 μM with glycine 1 μM at −70 mV) were antagonized by the tested cyclohexanes with IC_{50}s of 1.3–99 μM (Table 7). Peak and steady-state currents were affected to a similar degree making it unlikely that their effects were mediated at the $glycine_B$ site. Strong

support for the uncompetitive nature of this antagonism was provided by the clear use- and voltage-dependency of their blockade. The weaker antagonists showed faster kinetics and stronger voltage-dependency.

also agood correlation between potencies in antagonizing NMDA-induced inward currents and protection against NMDA-induced toxicity in vitro with anticonvulsive activity in vivo (corr. coeffs.>0.56. p<0.01).

TABLE 7

Mrz 2/	[^{3}H] MK-801 IC_{50} (uM) (μM)	SEM	Patch Clamp IC_{50} (uM)	SEM	Glut. Tox. IC_{50} (μM)	SD	MES ED_{50} mg/kg	C.L.
557	17.6	0.9	18.5	2.7	6.7	2.0	43.9	35.6–54.1
579	1.9	0.1	1.3	0.02	2.2	0.0	3.6	2.2–6.1
580	15.9	0.8	12.9	0.4	5.6	0.8	27.3	12.8–64
600	2.4	0.1	3.7	0.2	2.1	0.2	22.6	43.0–197
601	7.4	0.7	10.5	0.8	3.5	0.3	15.6	10.4–23.4
607	8.2	0.3	13.8	1.5	10.1	2.2	22.9	18.3–28.7
614	13.6	1.3	13.9	1.9	>10		23.5	15.7–34.9
615	2.5	0.1	2.9	0.1	2.3	0.1	6.1	3.4–10.7
616	15.0	0.4	34.2	4.6	9.1	2.1	24.0	15.6–36.8
617	51.8	3.9	57.4	7.3	>70		54.9	42.9–70.4
618	32.7	2.4	43.7	9.4	17.6	2.9	24.0	9.6–59.5
619	72.1	6.7	60.8	5.4	30.9	2.9	44.6	32.0–62.3
620	32.2	2.1	99.0	10.4	38.4	1.6	41.3	32.9–51.7
621	36.7	4.4	92.4	19.0	>100		36.9	22.6–60.3
622	15.0	0.6	64.8	11.7	19.3	8.1	21.0	16.1–27.5
623	3.3	0.2	3.7	0.7	4.5	0.6	13.1	9.9–17.2
624	15.4	1.2	31.0	3.6	2.7	0.6	47.2	41.8–53.2
625	46.3	8.1	244.9	40.1	39.4	6.3	129.8	42.5–395.6
626	11.6	1.5	9.6	2.0	19.0	3.3	41.2	29.9–56.7
627	70.3	3.3	209.7	1.0	26.6	5.7	43.9	30.3–63.7
628	35.6	4.4	125.5	0.8	27.3	4.5	73.2	33.6–159.4
629	39.4	2.4	218.6	1.6	>300		58.5	38.3–89.2
630	44.3	3.8	>100		>100		>30	
631	69.7	8.6	>100		>100		30.00	
632	2.0	0.2	6.4	0.6	10.9	0.4	11.04	7.7–15.8
633	6.8	0.5	13.9	3.2	5.4	0.9	8.78	3.6–21.4
634	15.5	1.0	10.8	2.6	19.0	3.5	>30	
635	7.8	0.4	21.0	4.6	8.2	1.4	31.59	21.3–46.8
639	3.3	0.3	7.4	1.0	5.7	0.4	5.5	3.8–9.0
640	3.7	0.6	14.6	1.2	8.3	0.4	8.2	5.7–11.8
641	184.5	26.7	>100		>100		>50	
642	10.2	1.6	42.5	6.5	29.3	3.3	8.04	5.1–12.7
643	3.6	0.5	13.5	1.7	12.0	0.9	18.65	10.8–32.2
644	3.8	3.7	4.1	1.8	4.3	0.4	52.98	27.8–100.8
645	85.1	30.6	20.4	3.6	>100		65.61	43.8–98.2
Memantine	0.7	0.11	2.3	0.3	1.3	0.7	6.9	5.4–8.8
Amantadine	20.4	5.4	71.0	11.1	20.7	0.7	184.0	122–279
MK-801	0.0026	0.0002	0.14	0.10	0.012	0.002	0.16	0.13–0.21

Excitotoxicity

Low μM concentrations of most cyclohexanes were effective neuroprotectants in vitro. with Mrz 2/579 seeming to be most potent in this regard (see Table 7). With most compounds full protection was obtained with 20 μM.

In vivo

Anticonvulsive Activity

All cyclohexane derivatives inhibited MES-induced convulsions in mice with ED_{50}s ranging from 3.6 to 50 mg/kg i.p. (Table 7). Selected compounds were also tested against PTZ- and NMDA-induced convulsions (see [20, 21] for methods) and showed comparable potency to the MES test (e.g., Mrz 2/579 had ED_{50}s in the PTZ- and NMDA tests of 5.5 and 3.7 mg/kg respectively). Their anticonvulsive potency was increased following i.v. administration (e.g., Mrz 2/579 ED_{50}=2.5 mg/kg). Mrz 2/579 was also active following s.c. and somewhat less potent following p.o. administration (ED_{50}s of 4.6 and 13.7 mg/kg respectively). At doses within the anticonvulsive range, myorelaxation (traction test) and ataxia (rotarod test) were observed with some cyclohexanes. For the majority of them, no acute lethality was seen at up to 50 mg/kg.

Correlation Analysis

There was a verygood cross correlation between all three in vitro assays (all corr. coeffs.>0.70. p<0.001). There was

Effects of cyclohexane derivatives and standard uncompetitive NMDA receptor antagonists on [^{3}H]-(−)-MK-801 binding. NMDA induced currents in patch clamp experiments, glutamate toxicity in cultured cortical neurones and MES-convulsions in vivo. Binding Ki values are means ±SEM of 3–5 experiments. IC_{50}s (±SEM) in patch clamp and glutamate toxicity experiments were determined from data from at least 3 concentrations producing between 15 and 85% inhibition and at least 5 cells per concentration. For MES-induced convulsions, values are ED_{50}s in mg/kg (95% confidence limits are shown in parentheses).

In addition, due at least in part to their amine substituent, the compounds of the present invention are also effective in non-NMDA indications, exhibiting immuno-modulatory activity, antimalaria potency, anti-Borna virus activity, and anti-Hepatitis C activity.

ADDITIONAL EXAMPLES AND PHARMACOLOGICAL UPDATES

Further 1-aminoalkylcyclohexane compounds, wherein the 1-aminogroup is cyclic, that is, wherein R^9 and R^9 together represent lower-alkylene —(CH2)x— wherein x is 2 to 5, inclusive, thereby presenting the 1-aminogroup

—NR^3R^9 in the form of a cyclic amine, are prepared in the following manner:

Preparation of N-(3-CyanoproPyl)-1,3,3,5,5-pentamethylcyclohexylamine (2)

A mixture of 1,3,3,5-pentamethylcyclahelaelydrochloride (1) (2.06 g, 10 mmol), 4-bromobutyronitrile (1.55 g, 10.5 mmol) and sodium carboate (3.18 g, 30 mmol) in tetrilydrofurin (50 ml) was refluxed for 85 h, then poured into water (100 ml) and extracted with ether (3*30 ml). The combined organic phases were washed with brine (20 ml) and dried over K_2CO_3. The solution was filtered and evaporated and the crtide product was purified by chromatography on silica gel eluting with hexane-ether (10:1), (6:1), (4:1) to give product 2 (1.86 g, 86%) a.s an colorless oil.

PMR spectrum: ($CDCl_3$, TMS) δ: 0.87 (6H, s, c-Hex 3,5-CH_3); 1.06 (3H, s, c-Hex 1-CH_3); 1.18 (6H, s, 3,5-H_3); 0.9–1.6 (7H, m, c-Hex ring protons and NH); 1.75 (2H, m, —CH_2—); 2.43 (2H, t, J=7 Hz, CH_2N) and 2.66 ppm, (2H, t, J=7 Hz, CH_2CN).

Preparation of MRZ 2/705, namely: N-(1,3,3,5,5-Pentamethylcyclohexyl) pyrrolidine hydrochloride (3)

N-(3-Cyanopropyl)-1,3,3,5,5-pentamethylcyclohexylamine (2) (1.2 g, 5.1 mmol) in ethanol (120 ml) and conc. HCl (4 ml) was hydrogenated over 10% Pd/C (250 mg) at 7 bar for 40 h (after 24 h additional portion of catalyst (260 mg) was added). The catalyst was removed by filtration through celite pad and solvent evaporated. The residue was treated with acltornitrile, the solids filtered off and the filtrate evaporated. The crude product was crystallized from ether to give N-(1,3,3,5,5-pentamethylcyclohexyl) pyrrolidine hydrochloride (3) (0.67 g, 49%) with m.p. 156–158° C.

PMR spectrum: (DMSO-d_6, TMS) δ: 0.97 (6H, s, 3,5-CH_3); 1.11 (6H, s, 3,5-CH_3); 0.8–1.4 (2H, cyclohexane 4-CH_2) 1.41 (3H, s, 1-CH_3); 1.69 (4H, m, cyclohexane 2,6-CH_2); 1.84 (4H, m, pyrrolidine 3,4-CH_2); 3.20) (4H, m, pyrrolidine 2,5-CH_2); 10.9 ppm (1H, br s, NH^+). Elemental analysis: $C_{15}H_{29}N^+HCl0.5H_2O$: Found (%) C, 67.7; H, 11.5; N, 5.5; Calculated (%) C, 67.0; H, 11.6; N, 5.2;

Additional 1-cyclic amino compounds are prepared in the same manner starting from the selected alkyl-substituted cyclohexylamine, usually in the form of an acid addition salt such as the hydrochloride, and the selected ω-bromoalkylnitrile, such as 4-bromobutyronitrile, 3-bromopropionitrile, 2-bromoacetonitrile, and 5-bromovaleronitrile, in the manner of the preceding preparation, first to produce the selected N-ω-cyanoalkyl-alkylcyclohexylamine compound and then to cyclize the N-ω-cyanoalkyl-alkylcyclohexylamine compound into the resulting N-(alkylcyclohexyl) cyclic amine compound, namely, the pyrrolidine, piperidine, or other cyclic amine compound, wherein the nitrogen atom and R^3 and R^9 together form the cyclic amine moiety, R^3 and R^9 together representing a lower-alkylene chain of the formula —$(CH_2)_x$— wherein x is 2 to 5, inclusive.

Thus N-(1,3,3,5,5-pentamethylcyclohexyl) piperidine hydrochloride or other acid addition salt and numerous other lower-alkyl substituted cyclohexanes having a 1-pyrrolidino or 1-piperidino group or other 1-cyclic amino group are prepared according to the invention, depending upon the ω-bromoalkylnitrile and the alkyl-substituted cyclohexylamine starting materials selected for the reaction.

UPDATED PHARMACOLOGICAL TABLES

The following Tables 8 and 9 present updated pharmacological results with various of the compounds of the present invention. The Tables show the following:

TABLE 8

MRZ #	MES ED_{50} mg/kg i.p.		TI Tract	TI Rot.	Min Lethality mg/kg i.p.
557	43.9	(35.6–54.1)	1.0	1.4	>70
579	3.6	(2.2–6.1)	2.9	5.0	108
580	27.3	(12.8–64)	1.6	1.3	50
600	22.6	(10.4–23.2)	0.6	0.9	50
601	15.6	(10.4–23.4)	1.5	1.5	50
607	22.9	(18.3–28.7)	1.3	1.7	50
614	23.5	(15.7–34.9)	1.9	1.6	>50
615	6.1	(3.4–10.7)	2.5	3.2	>50
616	24.0	(15.6–36.8)	1.0	1.4	>50
617	54.9	(42.9–70.4)	1.1	1.1	>50
618	24.0	(9.6–59.5)	1.2	1.1	>50
619	44.6	(32.0–62.3)	1.0	1.0	>50
620	41.3	(32.9–51.7)	1.6	1.5	>50
621	36.9	(22.6–60.3)	1.8	1.5	>60
622	21.0	(16.1–27.5)	1.1	1.7	50
623	13.1	(9.9–17.2)	1.4	1.8	>30
624	47.2	(41.8–53.2)	0.9	1.0	100
625	129.8	(42.5–395.6)	0.5	1.2	>70
626	41.2	(29.9–56.7)	1.1	1.0	>50
627	43.9	(30.3–63.7)	0.8	1.0	60
628	73.2	(33.6–159.4)	0.8	1.6	>60
629	58.5	(38.5–89.2)	0.9	0.9	100
630	>50		nc	nc	>50
631	30		nc	nc	>30
632	11.04	(7.7–15.8)	2.7	3.4	>30
633	8.78	(3.6–21.4)	2.4	3.0	108
634	>50		nc	nc	>30
635	31.59	(21.3–46.8)	1.3	1.4	>50
639	5.87	(3.8–9.0)	2.6	4.4	30
640	8.18	(5.7–11.8)	2.3	3.3	108
641	>50		nc	nc	>50
642	8.04	(5.1–12.7)	4.1	5.3	
643	18.65	(10.8–32.2)	1.3	2.4	>50
644	52.98	(27.8–100.8)	0.5	0.6	>35
645	65.61	(43.8–98.2)	0.6	0.6	
662	30.47	(18.0–51.6)	1.0	1.2	>40
680	34.5	(27.1–44.0)	0.7	1.1	>50
681	27.9	(18.2–42.6)	2.1	5.8	>50
682	7.6	(4.5–13.0)	2.7	3.6	>50
683	12.2	(6.3–23.5)	2.7	3.5	>50
705	9.55	(4.3–21.1)	3.9	5.4	>50
Memantine	6.9	(5.4–8.8)	2.9	2.5	>108
Amantadine	184.0	(122–279)	0.5	0.6	>324
MK-801	0.16	(0.13–0.21)	1.0	1.2	>108

TABLE 8

Effect of the present amino-alkyl-cyclohexane derivatives and standard uncompetitive NMDA receptor antagonists on convulsions induced by maximal electroshock (MES). Values are ED_{50}s in mg/kg (95% confidence limits are shown in parentheses). The therapeutic index (TI) was also calculated as the ED_{50} for inhibition of traction reflex (Tract.) impairment or rotarod failure (Rot.) divided by the ED_{50} for MES-induced seizure-induced convulsions. Most of the amino-alkyl-cyclohexane derivatives showed no acute toxicity, i.e., minimal lethal doses were above 50 mg/kg.

TABLE 9

MRZ	MK-801 Ki (μM)	SEM	Patch Clamp IC_{50} (μM)	SEM	Glut Tox IC_{50} (μM)	SEM
557	19.92	2.98	18.50	2.70	6.70	2.00
579	1.47	0.13	1.29	0.20	2.16	0.03
580	17.84	1.33	12.90	0.40	5.60	0.80
600	2.28	0.21	3.49	0.47	2.10	0.20
601	8.09	0.43	10.00	0.20	3.50	0.30
607	7.74	0.29	13.80	1.50	10.10	2.20
614	13.59	0.12	13.90	1.90	1.26	0.19
615	2.42	0.11	2.90	0.40	2.29	0.15
616	10.42	2.00	33.20	2.50	9.10	2.10
617	38.03	8.56	63.90	7.70	>70	nc
618	24.02	5.33	57.50	11.90	17.60	2.90
619	57.76	8.96	60.90	5.40	30.90	2.90
620	25.48	4.34	99.00	10.40	38.40	1.60
621	32.20	8.30	92.40	19.50	>100	nc
622	13.32	3.29	58.20	8.50	19.30	8.10
623	3.16	0.31	3.70	0.70	4.50	0.60
624	15.14	2.36	31.00	3.60	2.70	0.60
625	52.61	3.69	244.90	40.50	39.40	6.30
626	16.48	4.21	9.60	2.00	19.00	3.33
627	70.95	11.22	150.00	27.00	26.60	5.70
628	49.18	4.35	125.50	22.60	27.30	4.50
629	49.28	2.60	218.60	39.30	>300	nc
630	49.10	5.09	100.00	11.00	>100	nc
631	65.29	13.64	>100	nc	>100	nc
632	2.88	0.28	6.40	0.60	11.20	0.27
633	5.18	1.11	13.90	3.20	6.10	1.84
634	13.40	4.25	10.80	2.70	19.00	3.50
635	15.01	1.85	21.00	4.70	8.18	1.43
639	4.17	0.32	7.40	1.00	6.33	0.16
640	4.83	0.56	14.60	1.90	8.35	0.51
641	143.33	36.76	>100	nc	>100	nc
642	12.72	3.15	42.50	6.50	39.30	3.34
643	4.66	0.12	13.50	1.70	12.00	0.87
644	4.84	0.35	4.10	1.80	4.30	0.42
645	60.17	8.38	20.40	3.60	>100	nc
662	3.44	0.77	1.50	0.05	0.53	0.04
680	29.96	8.96	43.00	5.5	35.6	4.1
681	19.21	4.81	30.00	3.4	26.9	3.1
682	1.99	0.19	3.90	0.56	3.11	0.20
683	4.44		4.30	0.70	5.08	0.34
705	7.14	1.7	25.40	4.1	nt	nt
Amantadine	25.87	2.99	80.80	10.40	36.91	5.52
Memantine	2.45	0.91	2.87	0.44	1.40	0.10
MK-801	$6.56*10^{-3}$	$0.33*10^{-3}$	0.1400	0.1000	0.0130	0.0020

TABLE 9

Effect of amino-alkyl-cyclohexane derivatives and standard uncompetitive NMDA receptor antagonists on [^{3}H]-(+)-MK-801 binding, NMDA-induced currents in patch clamp experiments, andglutamate toxicity in cultured cortical neurones. Binding Ki values are means ±SEM of 3–5 experimeats and were determined according to the Cheng-Prusoff relationship with a Kd for MK-801 of 4.6 nM. IC_{50}s (±SEM) in patch clamp andglutamate toxicity experiments were determined from data from at least 3 concentrations producing between 15 and 85% inhibition and at least 5 cells/well per concentration.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1A and FIG. 1B show values obtained for these effects using MRZ 2/705.

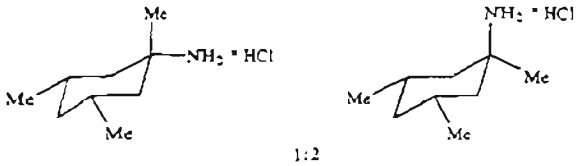
FIG. 2 shows the values obtained for various compounds of the invention and reference standards in the specific [^{3}H]-MK-801 binding test plotted against concentration.

Further research with respect to MRZ 2/616, 1-amino-1,3,5-trimethylcyclohexane, showed it to be a 1:2 mixture of the isomers 1,cis-3, cis-5-trimethyl- and 1,trans-3,trans-5-trimethylcyclohexylamine, which was separated in conventional manner into the individual pure enantiomeric forms MRZ 2/680, the 1-amino-1(trans),3(trans),5-trimethylcyclohexane and MRZ 2/681, 1-amino-1(cis),3(cis),5-trimethylcyclohexane as the hydrochloride and hydrochloride hydrate, respectively.

In addition, MRZ 2/632 and MRZ 2/633 were separated in conventional manner into their pure enantiomeric forms, MRZ 2/682 and MRZ 2/683, respectively 1-amino-(1R,5S) trans-3-ethyl-1,5,5-trimethylcyclohexane as the hydrochloride and 1-amino-(1S,5S)cis-3-ethyl-1,5,5-trimethylcyclohexane as the hydrochloride hydrate. All of these compounds, and their pure enantiomers, MRZ 2/616, MRZ 2/680, MRZ 2/681, MRZ 2/682 and MRZ 2/683, appear in the foregoing Tables along with the pharmacological data relating thereto.

The analytical certificates for these five (5) MRZ compounds follow:

MRZ 2/616



1.cis-3.cis-5-Trimethyl- and 1.trans-3.trans-5-trimethylcyclohexylamines hydrochlorides (~1.2)

Molecular formula: $C_9H_{19}N^*HCl$

Molecular weight: 177.7

Melting point: 280–282° C.

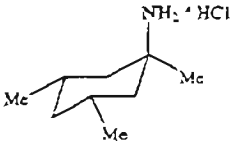
PMR spectrum: ($CDCl_3$, TMS) δ: 0.90 (6H, d, 5.5 Hz, 3.5-CH_3); 1.0–1.3 (2H, m, 4-CH_2); 1.44 and 1.50 (3H, both s, 1-CH_3); 1.55–2.4 (6H, m, 2-CH_2, 6-CH_2, 3-CH and 5-CH) and 8.25 ppm (3H, br s, NH_3^+).

Solubility: soluble in svater, chloroform.

Elemenital analysis: Found (%) C, 60.7; H, 11.5; N, 7.7; Calculated (%) C, 60.8; H, 11.3; N, 7.9;

Impurities: less than 2.5% (for free aniline: GC, MN-OV-1 (Fused Silica), 25 m*0.53 mm, d_f=1.0μ, 50–270° C. (10° C./min)).

MRZ 2/680



1.trans-3.trans-5-Trimethylcyclohexylamine hydrochloride

Molecular formula: $C_9H_{19}N^*HCl$

Molecular weight: 177.7

Melting point: >280° C.

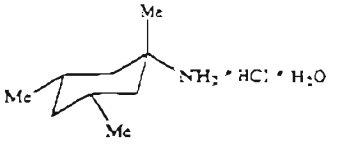
PMR spectrum: ($CDCl_3$, TMS) δ: 0.89 (6H, d, J=6 Hz, 3.5-CH_3); 0.9–2.3 (8H, m, ring protons); 1.44 (3H, S, 1-CH_3) and 8.25 ppm (3H, br s, NH_3^+).

Solubility: soluble in water, chloroform.

Elemental analysis: Found (%) C, 60.7; H, 11.7; N, 7.7; Calculated (%) C, 60.8; H, 11.3; N, 7.9;

Impurities: 2% (for free amine, GC, MN-OV-1 (Fused Silica), 25 m*0.53 mm, d_f=1.0μ, 50–270° C. (10° C./min)).

MRZ 2/681



1.cis-3.cis-5-Trimethylcyclohexylamine hydrochloride hydrate

Molecular formula: $C_9H_{19}N^*HCl^*H_2O$

Molecular weight: 195.7

Melting point: 237–238° C.

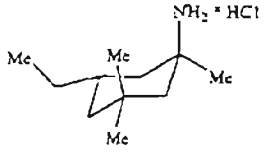
PMR spectrum: ($CDCl_3$, TMS) δ: 0.89 (6H, d, J=5.5 Hz, 3.5-CH_3); 0.9–2.3 (8H, m, ring protons); 1.47 (3H, s, 1-CH_3) and 8.3 ppm (3H, br s, NH_3^+).

Solubility: soluble in water, chloroform.

Elemental analysis: Found (%) C, 55.3; H, 11.6; N, 7.1; Calculated (%) C, 55.2; H, 11.3; N, 7.2;

Impurities: 1.5% (for free amine: GC, MN-OV-1 (Fused Silica), 25 m*0.53 mm, d_f=1.0μ, 50–270° C. (10° C./min)).

MRZ 2/682



(1R, 5S) trans-3-Ethyl-1.5.5-trimethylcyclohexylamine hydrochloride

Molecular formula: $C_{11}H_{23}N^*HCl$

Molecular weight: 205.8

Melting point: >280° C. (subl.)

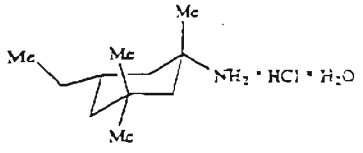
PMR spectrum: ($CDCl_3$, TMS) δ: 0.8–1.0 (m) and 0.91 (s, total 6H, 5-CH_{3eq} and CH_3-ethyl); 1.22 (3H, s, 5-CH_{3ax}); 1.44 (3H, s, 1-CH_3); 1.0–2.3 (9H, m, ring protons and CH_2-ethyl) and 8.2 ppm (3H, br s, NH_3^+).

Solubility: soluble in chloroform, poor soluble in water.

Elemental analysis: Found (%) C, 64.2; H, 11.9; N, 6.6; Calculated (%) C, 64.2; H, 11.8; N, 6.8;

Impurities: less than 1% (for free amine: GC, MN-OV-1 (Fused Silica), 25 m*0.53 mm, d_f=1.0 μ, 50–270° C. (10° C./min)).

MRZ 2/683



(1S, 5S) cis-3-Ethyl-1.5.5-trimethylcyclohexylamine hydrochloride hydrate

Molecular formula: $C_{11}H_{23}N^*HCl^*H_2O$

Molecular weight: 223.8

Melting point: 243–245° C.

PMR spectrum: ($CDCl_3$, TMS) δ: 0.88 (m) and 0.96 (s, total 9H, 5-CH_3 and CH_3-ethyl); 1.50 (3H, s, 1-CH_3); 1.0–2.15 (9H, m, ring protons and CH_2-ethyl) and 8.35 ppm (3H, br s, NH_3^+).

Solubility: soluble in chloroform, poor soluble in water.

Elemental analysis: Found (%) C, 59.9; H, 11.8; N, 6.2; Calculated (%) C, 59.0; H, 11.6; N, 6.3;

Impurities: less than 1% (for free amine: GC, MN-OV-1 (Fused Silica), 25 m*0.53 mm, d_f=1.0μ, 50–270° C. (10° C./min)).

In conclusion, from the foregoing, it is apparent that the present invention provides novel, valuable, and unpredict-

able applications and uses of the compounds of the present invention, which compounds comprise the active principle according to the present invention, as well as novel pharmaceutical compositions thereof and methods of preparation thereof and of treating therewith, all possessed of the foregoing more specifically-enumerated characteristics and advantages.

The high order of activity of the active agent of the present invention and compositions thereof, as evidenced by the tests reported, is indicative of utility based on its valuable activity in human beings as well as in lower animals. Clinical evaluation in human beings has not been completed, however. It will be clearly understood that the distribution and marketing of any compound or composition falling within the scope of the present invention for use in human beings will of course have to be predicated upon prior approval bygovernmental agencies, such as the U.S. Federal Food and Drug administration, which are responsible for and authorized to pass judgment on such questions.

Conclusions

The present 1-amino-alkylcyclohexanes represent a novel class of systemically-active, uncompetitive NMDA receptor antagonists with rapid blocking/unblocking kinetics and strong voltage-dependency. In view of their relatively low potency and associated rapid kinetics, they will be useful therapeutics in a wide range of CNS disorders which involve disturbances of glutamatergic transmission.

These compounds accordingly find application in the treatment of the following disorders of a living animal body, especially a human. 1. Acute excitotoxicity such as ischaemia during stroke, trauma, hypoxia, hypoglycemia, and hepatic encephalopathy. 2. Chronic neurodegenerative diseases such as Alzheimer's disease, vascular dementia, Parkinson's disease, Huntington's disease, multiple sclerosis, amyotrophic lateral sclerosis, AIDS-neurodegeneration, olivopontocerebellar atrophy, Tourette's syndrome, motor neurone disease, mitochondrial dysfunction, Korsakoff syndrome, Creutzfeldt-Jakob disease. 3. Other disorders related to long term plastic changes in the central nervous system such as chronic pain, drug tolerance, dependence and addiction (e.g., opioids, cocaine, benzodiazepines, and alcohol). 4. Epilepsy, tardive dyskinesia, schizophrenia, anxiety, depression, acute pain, spasticity, and tinnitus. 5. In addition, as already stated, due at least in part to their amine substituent, the compounds of the present invention are also effective in non-NMDA indications, exhibiting immunomodulatory activity, antimalaria potency, anti-Borna virus activity, and anti-Hepatitis C activity.

It is to be understood that the invention is not to be limited to the exact details of operation, or to the exact compositions, methods, procedures, or embodiments shown and described, as obvious modifications and equivalents will be apparent to one skilled in the art, and the invention is therefore to be limited only by the full scope which can be legally accorded to the appended claims.

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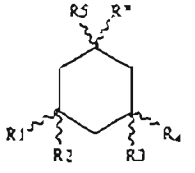
We claim:

1. A 1-aminoalkylcyclohexane compound selected from the group consisting of those of the formula



wherein R^* is $-(CH_2)_n-(CR^6R^7)_m-NR^8R^9$

wherein n+m=0, 1, or 2

wherein R^1 through R^7 are independently selected from the group consisting of hydrogen and lower-alkyl (1–6C), at least R^1, R^4, and R^5 being lower-alkyl, and wherein R^8 and R^9 are independently selected from the group consisting of hydrogen and lower-alkyl (1–6C) or together represent lower-alkylene $-(CH_2)_x-$ wherein x is 2 to 5, inclusive, and enantiomers, optical isomers, hydrates, and pharmaceutically-acceptable salts thereof.

2. A compound of claim 1 wherein R^1 through R^5 are methyl.

3. A compound of claim 1 wherein R^1 is ethyl.

4. A compound of claim 1 wherein R^2 is ethyl.

5. A compound of claim 1 wherein R^3 is ethyl.

6. A compound of claim 1 wherein R^4 is ethyl.

7. A compound of claim 1 wherein R^5 is ethyl.

8. A compound of claim 1 wherein R^5 is propyl.

9. A compound of claim 1 wherein R^6 or R^7 is methyl.

10. A compound of claim 1 wherein R^6 or R^7 is ethyl.

11. A compound of claim 1 wherein the compound is selected from the group consisting of

1-amino-1,3,5-trimethylcyclohexane,

1-amino-1(trans),3(trans),5-trimethylcyclohexane,

1-amino-1(cis),3(cis),5-trimethylcyclohexane,

1-amino-1,3,3,5-tetramethylcyclohexane,

1-amino-1,3,3,5,5-pentamethylcyclohexane,

1-amino-1,3,5,5-tetramethyl-3-ethylcyclohexane,

1-amino-1,5,5-trimethyl-3,3-diethylcyclohexane,

1-amino-1,5,5-trimethyl-cis-3-ethylcyclohexane,

1-amino-(1S,5S)cis-3-ethyl-1,5,5-trimethylcyclohexane,

1-amino-1,5,5-trimethyl-trans-3-ethylcyclohexane,

1-amino-(1R,5S)trans-3-ethyl-1,5,5-trimethylcyclohexane,

1-amino-1-ethyl-3,3,5,5-tetramethylcyclohexane,

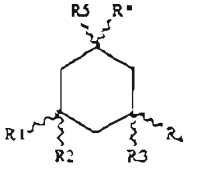
1-amino-1-propyl-3,3,5,5-tetramethylcyclohexane,

N-methyl-1-amino-1,3,3,5,5-pentamethylcyclohexane,

N-ethyl-1-amino-1,3,3,5,5-pentamethylcyclohexane, and

N-(1,3,3,5,5-pentamethylcyclohexyl) pyrrolidine, and optical isomers, enantiones, hydrates and pharmaceutically-acceptable salts of any of the foregoing.

12. An NMDA-receptor antagonist pharmaceutical composition comprising an effective NMDA-receptor antagonistic amount, or an effective immunomodulatory, antimalarial, anti-Borna virus, or anti-Hepatitis C amount, of a 1-aminoalkylcyclohexane compound selected from the group consisting of those of the formula



wherein R^* is $-(CH_2)_n-(CR^6R^7)_m-NR^8R^9$

wherein n+m=0, 1, or 2

wherein R^1 through R^7 are independently selected from the group consisting of hydrogen and lower-alkyl (1–6C), at least R^1, R^4, and R^5 being lower-alkyl, and wherein R^8 and R^9 are independently selected from the group consisting of hydrogen and lower-alkyl (1–6C) or together represent lower-alkylene $-(CH_2)_x-$ wherein x is 2 to 5, inclusive, and optical isomers, enantiomers, hydrates, and pharmaceutically-acceptable salts thereof, in combination with one or more pharmaceutically-acceptable diluents, excipients, or carriers.

13. A pharmaceutical composition of claim 12 wherein R^1 through R^5 are methyl.

14. A pharmaceutical composition of claim 12 wherein R^1 is ethyl.

15. A pharmaceutical composition of claim 12 wherein R^2 is ethyl.

16. A pharmaceutical composition of claim 12 wherein R^3 is ethyl.

17. A pharmaceutical composition of claim 12 wherein R^4 is ethyl.

18. A pharmaceutical composition of claim 12 wherein R^5 is ethyl.

19. A pharmaceutical composition of claim 12 wherein R^5 is propyl.

20. A pharmaceutical composition of claim 12 wherein R^6 or R^7 is methyl.

21. A pharmaceutical composition of claim 12 wherein R^6 or R^7 is ethyl.

22. A pharmaceutical composition of claim 12 wherein the compound is selected from the group consisting of

1-amino-1,3,5-trimethylcyclohexane,

1-amino-1(trans),3(trans),5-trimethylcyclohexane,

1-amino-1(cis),3(cis),5-trimethylcyclohexane,

1-amino-1,3,3,5-tetramethylcyclohexane,

1-amino-1,3,3,5,5-pentamethylcyclohexane,

1-amino-1,3,5,5-tetramethyl-3-ethylcyclohexane,

1-amino-1,5,5-trimethyl-3,3-diethylcyclohexane,

1-amino-1,5,5-trimethyl-cis-3-ethylcyclohexane,

1-amino-(1S,5S)cis-3-ethyl-1,5,5-trimethylcyclohexane,

1-amino-1,5,5-trimethyl-trans-3-ethylcyclohexane,

1-amino-(1R,5S)trans-3-ethyl-1,5,5-trimethylcyclohexane,

1-amino-1-ethyl-3,3,5,5-tetramethylcyclohexane,

1-amino-1-propyl-3,3,5,5-tetramethylcyclohexane,

N-methyl-1-amino-1,3,3,5,5-pentamethylcyclohexane,

N-ethyl-1-amino-1,3,3,5,5-pentamethylcyclohexane, and

N-(1,3,3,5,5-pentamethylcyclohexyl) pyrrolidine, and optical isomers, enantiomers, hydrates and pharmaceutically-acceptable salts of any of the foregoing.

* * * * *

3. Pielikums

The synthesis of 3-amino-3-methylbicyclo[3.3.1]nonanes: *Endo*-selectivity in the Ritter reaction of 1,3,5,7α-tetramethylbicyclo[3.3.1]nonan-3-ol

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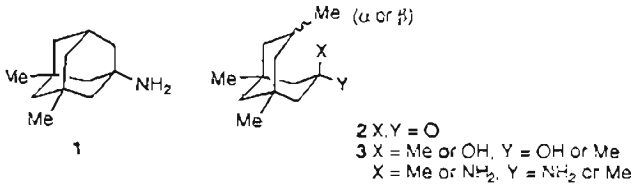
Received (in Cambridge, UK) 2nd June 1999, Accepted 20th September 1999

1,3,5,7α- and 1,3,5,7β-Tetramethylbicyclo[3.3.1]nonan-3-ols **3a** and **3b** were prepared from the corresponding ketones **2a** and **2b**. 7α-Methyl isomer **3a** gave selectively *endo*-3α-*N*-formylaminobicyclononane **10** in the Ritter reaction with trimethylsilyl cyanide. 7β-Methyl epimer **3b** suffered water elimination resulting in bicyclo[3.3.1]non-2-ene **12** under the same reaction conditions. The *endo*-amide structure was confirmed by X-ray analysis..

Introduction

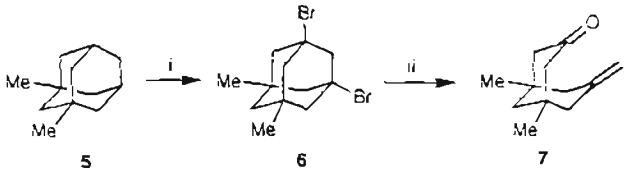
The therapeutic value of *N*-methyl-D-aspartate (NMDA) receptor antagonists for the treatment of central nervous system disorders has been discussed for many years.[1] The high-affinity NMDA receptor antagonists provoke undesirable side effects at therapeutic concentrations. However, Memantine **1** (1-amino-3,5-dimethyladamantane) possessing moderate receptor affinity, acts as an uncompetitive NMDA receptor antagonist and has been used for many years in the treatment of dementia.[1] Thus, clinical experience with Memantine **1** has shown that it is possible to develop NMDA receptor antagonists which do not activate receptors pathologically and retain their physiological activity. During the investigations of *N*-methyl-D-aspartate receptor ion channel blockers, Memantine **1** structural isomers, compounds of increased lipophilicity with shapes similar to Memantine **1**, have been sought.[2] Thus, it was necessary to develop a synthetic route toward 1,3,5,7-tetramethylbicyclo-[3.3.1]nonan-3-amine **4** isomers (X = CH_3, Y = NH_2 or *vice versa*).



Up to now the successful introduction of a nitrogen functionality at the tertiary C-3 carbon atom in bicyclo[3.3.1]nonane has not been reported. Moreover, nucleophilic additions to the carbonyl group in this system have been found to be quite difficult. Fortunately, recent studies of organocerium reagent addition to bicyclo[3.3.1]nonan-3-one demonstrated the possibility of developing the synthesis of the corresponding alcohols **3** from ketones **2**. Our synthetic efforts were, therefore, focussed on the Ritter reaction of tertiary alcohols **3**. Herein we report the first synthesis of 3-methyl-3-aminobicyclo[3.3.1]nonane derivatives and evidence that the Ritter reaction proceeds *endo*-selectively.

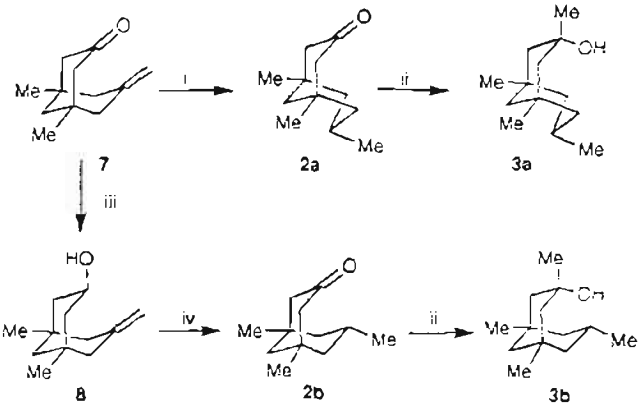
Results and discussion

7-Methylene-1,5-dimethylbicyclononan-3-one **7** can be obtained in two steps by bromination of 1,3-dimethyladamantane **5**[3] and by subsequent Grob fragmentation of 1,3-dibromo-5,7-dimethyladamantane **6**[4] (Scheme 1). Ketone **7** served as a starting material for the preparation of both 1,5,7α- and 1,5,7β-trimethylbicyclo[3.3.1]nonan-3-ones **2a** and **2b**.



Scheme 1 *Reagents and conditions*: i, Br_2, Fe, 83%; ii, NaOH, 79%.

Hydrogenation of unsaturated ketone **7** using a modified literature procedure[5] provided 1,5,7α-trimethylbicyclononan-3-one **2a** (Scheme 2). 3,5-Dimethyladamantan-1-ol was isolated as a by-product in this reaction. With a sample of isomeric ketone **2b** in hand we were able to estimate that the hydrogenation was highly selective, *i.e.* less than 2% of 7β-methyl isomer **2b** was detected by GC analysis. 1,5,7β-Trimethylbicyclononanone **2b** was obtained by the known procedure involving Meerwein–Pondorf–Verley reduction[6] of unsaturated ketone **7** and a subsequent acid catalyzed intramolecular proton transfer[7] in 7-methylene-1,5-dimethylbicyclo[3.3.1] nonan-3β-ol **8** (Scheme 2).



Scheme 2 *Reagents and conditions*: i, H_2, PtO_2, 34%; ii, "$MeCeCl_2$", 97% of both **3a** and **3b**; iii, $Al(OPr^i)_3$, 57%; iv, 75% H_2SO_4, 73%.

The next step involved the introduction of a methyl group at the C-3 position of bicyclononane. Bicyclo[3.3.1]nonan-3-one itself has been shown to be absolutely inert toward alkylmagnesium and -lithium reagents,[8] while organolanthanoid species were found to add to the carbonyl group more effi-

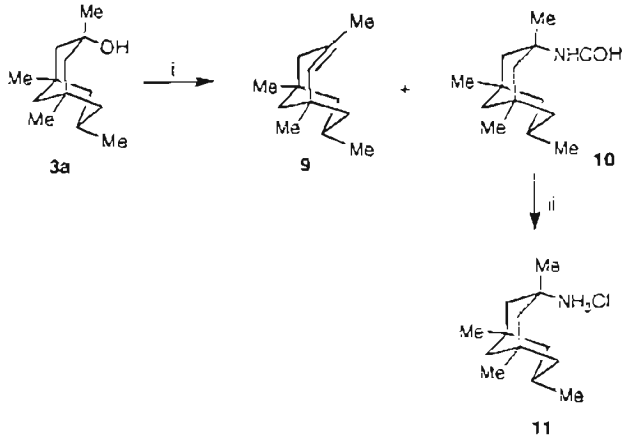
Table 1 Conversion of isomeric bicyclononanes 2 to tertiary alcohols 3 by organometallic reagents

Entry	Reaction conditions	Conversion to alcohols (%)[a] 3a	3b
1	MeMgI/Et_2O	50	9
2	MeLi/THF/cumene	70	40
3	MeMgI/$CeCl_3$/THF	100	100

[a] The conversion was determined from alcohol/ketone ratio by GC.

ciently.[9] 1,5,7-Trimethylbicyclononanones **2a** and **2b** displayed low to moderate conversion in reactions with methylmagnesium iodide and methyllithium, providing mixtures of the desired alcohols and starting ketones. Using the reagent prepared from methylmagnesium iodide and cerium trichloride, complete reaction was observed with both substances to give alcohols **3a** and **3b** in excellent yields (Table 1).

To introduce the amino group both alcohols **3a** and **3b** were used in the Ritter reaction with sulfuric acid and trimethylsilyl cyanide[10] as a hydrogen cyanide source (Scheme 3). Thus,



Scheme 3 *Reagents and conditions*: i, TMSCN, H_2SO_4, 34% of **9** and 55% of **10**; ii, H_3O^+, 71%.

1,3β,5,7α-tetramethylbicyclo[3.3.1]nonan-3α-ol **3a** gave 1,3,5,7β-tetramethylbicyclo[3.3.1]non-2-ene **9** and *N*-formyl-1,3,5,7-tetramethylbicyclo[3.3.1]nonan-3-amine **10** (34% of **9** and 55% of **10** by GC). The GC analysis of the reaction mixture indicated that only one amide isomer was formed. The other peaks registered with similar retention time were of negligible integral intensity (<1%). The ^1H NMR spectrum of the reaction product **10** was somewhat complicated due to the *cis–trans* isomerism of the formyl group, as could be seen from the different spin coupling constants of the formyl group protons. However, hydrolysis of formamide **10** undoubtedly gave one amine isomer **11** according to GC analysis, and ^1H and ^{13}C NMR spectra. As the correct stereochemical assignment of the formamido group could not be determined from simple ^1H NMR experiments due to the lack of any vicinal spin couplings, crystals of *N*-formyl derivative **10** were prepared for a single crystal X-ray analysis. This revealed two independent molecules (*a* and *b*) in the asymmetric unit cell (Fig. 1). These molecules differ in the orientation of the formylamino group. The torsion angles C5–C4–N3–C2 for the molecules *a* and *b* are −174.5(7) and 59.2(8)°, respectively. The bicyclo[3.3.1]nonane framework adopts a chair–boat conformation with the formamido group in the axial position of the chair.

There is little information in the literature about the stereochemistry of the Ritter reaction to explain the selective formation of **10**. Studies have been carried out only with 4-substituted cyclohexyl cations, showing the preference for axial nitrile

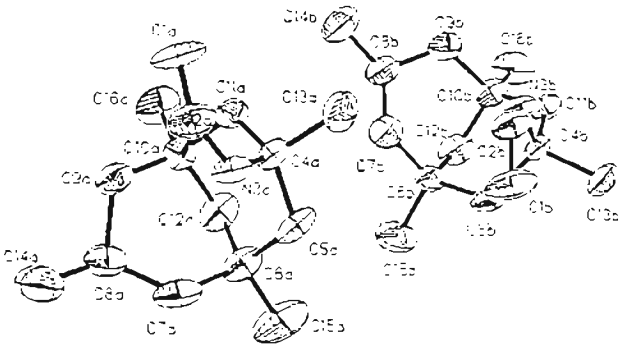


Fig. 1 Crystal structure of *N*-formyl-1,3,5,7β-tetramethylbicyclo-[3.3.1]nonan-3α-amine **10**.

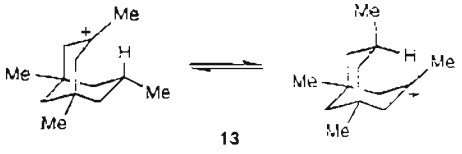
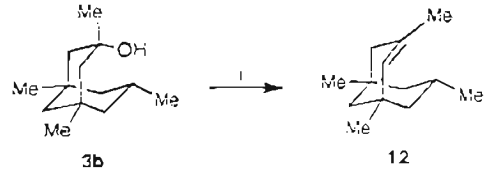


Fig. 2 Transannular hydride transfer in **13**.

attack.[11–13] Such a reaction course was explained by torsional strain caused by the 2,6-axial hydrogens, analogously to the nucleophilic addition to cyclohexanones.[11,12] Alternatively, Ichikawa suggested that the axial product resulted from the *trans*-antiparallel electrophilic addition of H^- and CH_3CN to the olefinic bond.[13]

It is known that 3α-methylbicyclo[3.3.1]nonanone undergoes predominately *exo* attack of nucleophiles.[5] It is reasonable to assume that the capture of nitrile by the carbocation should also occur predominately from the *exo* face. Obviously, the selective *endo* product **10** formation cannot be explained by steric discrimination as the bicyclononyl cation should adopt the same conformation as the parent bicyclononanone. It is possible that *trans*-antiparallel addition as suggested by Ichikawa could be better rationalized as discrimination of the carbocation faces due to the differing C–C and C–H hyperconjugation.[14] The effect of hyperconjugation should thus override the steric factors. It is evident, however, that a more detailed investigation of the Ritter reaction stereochemistry should be carried out.

7β-Methylbicyclononanol **3b**, unlike its epimer **3a**, gave 1,3,5,7β-tetramethylbicyclo[3.3.1]non-2-ene **12** as sole product (93% by GC of the reaction mixture) and no formamide was isolated under the same Ritter reaction conditions (Scheme 4).



Scheme 4 *Reagents and conditions*: i, TMSCN, H_2SO_4, 66%.

It has been shown that the 7β-methylbicyclononan-3-yl cation **13** undergoes rapid transannular hydride transfer and exists in the double chair conformation (Fig. 2).[15] As a result of this, the *endo* face becomes inaccessible. The different reactivities of alcohols **3a** and **3b** provide additional evidence that amide formation from an obviously sterically unfavoured nitrile attack from the *endo* side of the carbocation is much more rapid than that from the *exo* side. This phenomenon requires an explanation which can be provided only on the basis of more extended studies. The results obtained for the Ritter reaction of both bicyclononanols **3a** and **3b** show that the stereoselectivity of

amide formation does not follow the rules of nucleophilic addition to the carbonyl group.[11]

Experimental

Melting points were determined in capillary tubes on a Gallenkamp apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer 580B spectrometer. Mass spectra were registered on a Hewlett Packard HP 6890 Series GC system. Microanalyses were performed on a Carlo Erba Instrument EA1108. ^1H and ^{13}C NMR spectra were determined on a Varian Mercury 200BB spectrometer for solutions in $CDCl_3$ with TMS as internal standard. Chemical shifts are recorded as δ values in ppm. J Values are given in Hz. Reaction mixture analyses were made and the purity of all products were determined by GC analysis [MN-OV-1 (Fused Silica), 25 m × 0.53 mm, d_f = 1.0 μ, 50–270 °C (10 °C min^{-1})]. Preparative chromatography was carried out on Kieselgel 63–100 μm by the flash column method.[16] TLC analyses were performed on Kieselgel 60 F_{254} plates (Merck). Eluent: hexane–ethyl acetate, visualization agent: iodine vapors. Ether refers to diethyl ether. Petroleum ether refers to the fractions of bp 40–60 °C. Evaporation of solvent indicates evaporation under reduced pressure using a rotary evaporator. Tetrahydrofuran (THF) was distilled from sodium and benzophenone. Ether and acetonitrile (CH_3CN) were distilled from calcium hydride. Petroleum ether, methanol and ethyl acetate were distilled prior to use. Starting material 1,3-dimethyladamantane **5** and all the reagents were purchased from Aldrich.

1,3-Dibromo-5,7-dimethyladamantane 6

Iron powder (1.5 g) was added to bromine (65 ml) cooled in an ice bath. Neat 1,3-dimethyladamantane **5** (24.5 g, 150 mmol) was added dropwise to the reaction mixture during 1 h. The mixture was stirred for 1.5 h at room temperature then poured onto ice (0.5 kg) and carbon tetrachloride (250 ml) was added. Excess bromine was reduced with sodium metabisulfite. The organic layer was separated and the aqueous phase was extracted twice with chloroform (100 ml). The combined organic layers were washed with brine, saturated $NaHCO_3$ and dried ($CaCl_2$). Solvent evaporation gave a crude product which was treated with methanol (50 ml). Crystals were collected by filtration and washed with methanol to provide **6** (39.9 g, 83%), mp 106–107 °C (Found: C, 44.88; H, 5.55. $C_{12}H_{18}Br_2$ requires C, 44.75; H, 5.63%); m/z 241 (100%, [M − Br]$^+$); δ_H(200 MHz, $CDCl_3$) 0.92 (6H, s, 5,7-CH_3), 1.23 (2H, s, 6-H_2), 1.97 (8H, s, 4,8,9,10-H_2), 2.69 (2H, s, 2-H_2); δ_C(50 MHz, $CDCl_3$) 28.86, 38.51, 47.95, 50.67, 53.17, 57.35.

1,5-Dimethyl-7-methylenebicyclo[3.3.1]nonan-3-one 7[17]

1,3-Dibromo-5,7-dimethyladamantane **6** (21.6 g, 67 mmol) was heated in a mixture of dioxane (200 ml) and 1 M NaOH (200 ml) in a steel autoclave at 180 °C for 20 h. Water (200 ml) was added to the reaction mixture and the product was extracted with ether (3 × 150ml). The combined extracts were washed with brine (100ml) and dried ($CaCl_2$). Filtration and solvent evaporation gave an oily residue which was distilled at reduced pressure (113–116 °C/12 mmHg) to provide **7** (9.4 g, 79%) as an oil (Found: C, 81.04; H, 10.06. $C_{12}H_{18}O$ requires C, 80.85; H, 10.18%); m/z 178 (10%, M$^+$); δ_H(200 MHz, $CDCl_3$) 1.06 (6H, s, 1,5-CH_3), 1.50 (2H, td, J 13.2 and 2.0, 9-H), 1.62 (2H, td, J 13.2 and 2.0, 9-H), 1.97 (2H, m, 6,8-H_{ax}), 1.98 (2H, m, 2,4-H_{ax}), 2.40 (2H, dd, J 13.4 and 2.0, 6,8-H_{eq}), 2.20 (2H, dd, J 16.2 and 2.0, 2,4-H_{eq}), 4.75 (2H, t, J 1.4, =CH_2); δ_C(50 MHz, $CDCl_3$) 30.26, 34.78, 47.24, 47.78, 53.05, 113.94, 142.79, 210.93.

1,5,7α-Trimethylbicyclo[3.3.1]nonan-3-one 2a

A solution of unsaturated ketone **7** (0.7 g, 3.9 mmol) in acetic acid (7 ml) was hydrogenated (1 atm) over PtO_2 (70 mg) for 7 h. Catalyst was filtered off, water (20 ml) was added and the filtrate extracted with ether (30 ml). The organic phase was washed with saturated aqueous $NaHCO_3$ and dried ($MgSO_4$). After evaporation of ether the residue was purified by column chromatography eluting with 4% ethyl acetate in petroleum ether to give **2a** (0.24 g, 34%) as an oil (Found: C, 79.78; H, 11.15. $C_{12}H_{20}O$ requires C, 79.94; H, 11.18%); m/z 180 (8%, M$^+$); δ_H(200 MHz, $CDCl_3$) 0.80 (3H, d, J 7.4, 7-CH_3), 1.05 (6H, s, 1,5-CH_3), 0.7–1.9 (8H, m, 2,4-H_{ax}, 6,8,9-H_2), 1.9–2.4 (3H, m, 2,4-H_{eq}, 7-H); δ_C(50 MHz, $CDCl_3$) 24.75, 32.43, 33.82, 43.13, 44.8, 55.96; ν_{max}(thin film)/cm^{-1} 1709 (C=O).

Further elution with 30% ethyl acetate in petroleum ether gave 3,5-dimethyladamantan-1-ol (0.24 g) identical with an authentic sample.

1,5-Dimethyl-7-methylenebicyclo[3.3.1]nonan-3β-ol 8

The mixture of unsaturated ketone **7** (1g, 5.6 mmol) and aluminium triisopropoxide (2.64 g, 12.9 mmol) in toluene (20 ml) was refluxed for 17 h. Aqueous NaOH (10 ml of a 10% solution) was added and the resulting two phase mixture was stirred for 2 h at room temperature. The organic layer was separated, the aqueous layer extracted with ether (2 × 20 ml), and the combined extracts were washed with brine and dried ($MgSO_4$). Evaporation of the solvent gave crude product which was purified by column chromatography eluting with 10% ethyl acetate and then with 20% ethyl acetate in petroleum ether to give **8** (0.57 g, 57%), mp 94–96 °C (Found: C, 79.81; H, 11.17. $C_{12}H_{20}O$ requires C, 79.94; H, 11.18%); m/z 180 (21%, M$^+$); δ_H(200 MHz, $CDCl_3$) 0.95 (6H, s, 1,5-CH_3), 0.8–1.20 (4H, m, 6,8-H_{ax} and 9-H_2), 1.24 (1H, s, OH), 1.7–2.3 (4H, m, 2,4-H_{ax} and 6,8-H_{eq}), 2.16 (2H, d, J 14.2, 2,4-H_{eq}), 4.45–4.7 (3H, m, =CH_2 and 3-H); δ_C(50 MHz, $CDCl_3$) 31.48, 34.57, 46.56, 47.79, 48.34, 48.63, 108.49, 148.32.

1,5,7β-Trimethylbicyclo[3.3.1]nonan-3-one 2b

Unsaturated alcohol **8** (0.45 g, 2.5 mmol) was stirred for 7 h in 75% H_2SO_4 (13 ml) at room temperature. Water (30 ml) was added and the mixture was extracted with hexane (50 ml and 25 ml). The organic layer was washed with saturated $NaHCO_3$ (25 ml) and water (25ml), and dried ($MgSO_4$). After evaporation of solvent the residue was passed through a short silica gel column eluting with 10% ethyl acetate in petroleum ether. Crystalline product **2b** (0.33g, 73%) was obtained, mp 48–50 °C (Found: C, 80.02; H, 11.11. $C_{12}H_{20}O$ requires C, 79.94; H, 11.18%); m/z 180 (11%, M$^+$); δ_H(200 MHz, $CDCl_3$) 0.81 (3H, d, J 5.8, 7-CH_3), 0.7–1.0 (2H, m, 9-H_2), 1.00 (6H, s, 1,5-CH_3), 1.2–1.35 (1H, m, 7-H), 1.4–1.6 (4H, m, 6,8-H_2), 2.01 (2H, d, J 15.4, 2,4-H_{ax}), 2.22 (2H, dd, J 16.3 and 2.0, 2,4-H_{eq}); δ_C(50 MHz, $CDCl_3$) 26.61, 30.96, 34.86, 47.27, 47.79, 47.71, 53.06; ν_{max}(Nujol)/cm^{-1} 1708 (C=O).

General procedure for synthesis of 1,3,5,7-tetramethylbicyclo-[3.3.1]nonan-3α-ols 3a and 3b

$CeCl_3 \cdot 7H_2O$ (4.0 mmol) was quickly powdered in a mortar and heated *in vacuo* (4 mmHg) while raising the temperature gradually to 140 °C, and then kept at this temperature for 2 h. After cooling under an argon atmosphere, THF (17 ml) was added and the suspension obtained was allowed to stir overnight at room temperature. The suspension was cooled to 3 °C and MeMgI (4.2 ml of a 0.95 M solution in ether, 4.0 mmol) was added. After the mixture had been stirred for 1 h at 3 °C, a solution of ketone **2a** or **2b** (2 mmol) in THF (5 ml) was added dropwise. After 15 min, saturated aq. NH_4Cl was added. The aqueous layer was extracted with ether (2 × 20 ml) and the combined extracts were washed with brine and dried over $MgSO_4$. The solution was filtered and the solvent evaporated. The residue was passed through a short silica gel column eluting with ether to give essentially pure **3a** or **3b**.

1,3β,5,7α-Tetramethylbicyclo[3.3.1]nonan-3α-ol 3a. Yield 97%; mp 87–89 °C (Found: C, 79.70; H, 12.26. $C_{13}H_{24}O$ requires C, 79.53; H, 12.32%); *m/z* 196 (0.1%, M^{+}), 181 (4, $[M - CH_3]^{+}$), 178 (5, $[M - H_2O]^{+}$); δ_H(200 MHz, $CDCl_3$) 0.52 (1H, d, *J* 12.6, 9-H), 0.81 (3H, d, *J* 5.8, 7-CH_3), 0.7–0.9 (1H, m, 9-H), 0.90 (6H, s, 1,5-CH_3), 1.15 (3H, s, 3-CH_3), 1.0–1.7 (10H, m, 2,4,6,8-H_2, 7-H and OH); δ_C(50 MHz, $CDCl_3$) 22.03, 26.01, 30.36, 34.01, 35.21, 40.74, 44.61, 53.17, 72.33.

1,3β,5,7β-Tetramethylbicyclo[3.3.1]nonan-3α-ol 3b. Yield 97%; mp 72–74 °C (Found: C, 79.64; H, 12.30. $C_{13}H_{24}O$ requires C, 79.53; H, 12.32%); *m/z* 196 (0.1%, M^{+}), 181 (14, $[M - CH_3]^{+}$), 178 (4, $[M - H_2O]^{+}$); δ_H(200 MHz, $CDCl_3$) 0.80 (3H, d, *J* 6.6, 7-CH_3), 0.86 (6H, s, 1,5-CH_3), 0.6–1.1 (4H, m, 9-H_2 and 6,8-H_{ax}), 1.06 (1H, s, OH), 1.24 (3H, s, 3-CH_3), 1.3–1.6 (6H, m, 2,4-H_2 and 6,8-H_{eq}), 2.75 (1H, m, 7-H); δ_C(50 MHz, $CDCl_3$) 23.68, 24.73, 30.36, 32.22, 33.48, 37.04, 47.77, 48.05, 51.30, 69.79.

Ritter reaction of 1,3,5,7-tetramethylbicyclo[3.3.1]nonan-3α-ols 3a and 3b

To the mixture of alcohol **3a** or **3b** (0.59 g, 3 mmol) and TMSCN (0.80 ml, 6 mmol) was added acetic acid (0.5 ml) and the mixture was cooled to 3 °C. Sulfuric acid (0.48 ml; 9 mmol) was added dropwise (25 min). The reaction mixture was allowed to warm to room temperature, stirred for 24 h and poured into ice water (20 ml). The resulting mixture was neutralized with 20% NaOH and extracted with ether (2 × 20 ml). The combined extracts were dried ($MgSO_4$) and the solvent evaporated. The reaction products were separated by column chromatography eluting with petroleum ether to give bicyclonene **9** or **12**, then with 30% ethyl acetate in petroleum ether to obtain amide **10**.

1,3,5,7α-Tetramethylbicyclo[3.3.1]non-2-ene 9. A volatile liquid (34%) (Found: C, 87.74; H, 12.35. $C_{13}H_{22}$ requires C, 87.56; H, 12.44%); *m/z* 178 (6%, M^{+}); δ_H(200 MHz, $CDCl_3$) 0.87 (3H, d, *J* 6.8, 7-CH_3), 0.92 and 0.94 (total 6H, both s, 1,5-CH_3), 1.57 (3H, br s, 3-CH_3), 0.8–1.9 (9H, m, ring protons), 5.15 (1H, br s, 2-H); δ_C(50 MHz, $CDCl_3$) 22.30, 23.37, 26.19, 30.42, 30.63, 32.03, 32.84, 43.00, 44.23, 45.09, 45.64, 131.84, 133.39.

***N*-Formyl-1,3β,5,7α-tetramethylbicyclo[3.3.1]nonan-3α-amine 10.** Yield 55%; mp 108–110 °C (Found: C, 75.31; H, 11.24; N, 6.23. $C_{14}H_{25}NO$ requires C, 75.28; H, 11.28; N, 6.27%); *m/z* 223 (2%, M^{+}); δ_H(200 MHz, $CDCl_3$) 0.93 and 0.94 (total 6H, both s, 1,5-CH_3), 0.57–2.2 (17H, m, ring protons and 3,7-CH_3), 5.2 and 5.6 (total 1H, both br s, NH), 8.03 and 8.33 (total 1H, both d, *J* 2.6 and 12.8, CHO); δ_C(50 MHz, $CDCl_3$) 21.83, 25.10, 25.68, 30.47, 31.54, 33.69, 36.00, 40.42, 40.53, 44.69, 49.99, 52.29, 54.82, 160.66, 160.84.

1,3,5,7β-Tetramethylbicyclo[3.3.1]non-2-ene 12. A volatile liquid (66%) (Found: C, 87.69; H, 12.38. $C_{13}H_{22}$ requires C, 87.56; H, 12.44%); *m/z* 178 (7%, M^{+}); δ_H(200 MHz, $CDCl_3$) 0.80 (3H, d, *J* 7.1, 7-CH_3), 0.91 and 0.94 (total 6H, both s, 1,5-CH_3), 0.55–1.6 (7H, m, 6,8,9-H_2 and 7-H), 1.63 (3H, br s, 3-CH_3), 1.63 and 1.80 (total 2H, both d, *J* 18, 4-H_2), 5.03 (1H, br s, 2-H); δ_C(50 MHz, $CDCl_3$) 22.21, 22.82, 26.82, 29.51, 31.67, 32.06, 32.16, 34.17, 44.25, 46.48, 47.24, 130.21, 134.58.

1,3β,5,7α-Tetramethylbicyclo[3.3.1]nonan-3α-amine hydrochloride 11

Formamide **10** (0.39 g, 1.75 mmol) was refluxed in 20% aqueous H_2SO_4 (4.2 ml) for 6 h. The reaction mixture was poured onto ice and neutralized with 20% NaOH. The product was extracted with ether (2 × 25 ml), and the combined extracts were dried over NaOH and filtered. To the filtrate was added HCl (1.5 ml of a 2 M solution in ether) and the solvent as well as the excess of HCl were removed *in vacuo*. The residue was treated with CH_3CN and filtered to provide **12** as white crystals (0.29 g, 71%), mp 284–285 °C (Found: C, 67.16; H, 11.39; N, 5.93. $C_{13}H_{25}N$·HCl requires C, 67.36; H, 11.31; N, 6.04%); *m/z* 195 (1%, M^{+}); δ_H(200 MHz, $CDCl_3$) 0.67 (1H, d, *J* 13, 9-H), 0.96 (6H, s, 1,5-CH_3), 1.03 (3H, d, *J* 6.5, 7-CH_3), 1.54 (3H, s, 3-CH_3), 0.8–1.9 (8H, m, 2,4-H_{ax}, 6,8-H_2, 7,9-H), 2.07 (2H, d, *J* 14.3, 2,4-H_{eq}), 8.2 (3H, br s, NH_3^{+}); δ_C(50 MHz, $CDCl_3$) 21.20, 26.18, 30.18, 32.15, 33.04, 42.43, 43.11, 49.48, 55.11.

Crystal structure determination for compound 10

$C_{14}H_{25}NO$, $M = 223.35$, triclinic, $a = 8.885(2)$, $b = 12.104(2)$, $c = 13.479(3)$ Å, $\alpha = 88.19(3)$, $\beta = 84.38(3)$, $\gamma = 85.53(3)°$, $V = 1437.5(5)$ Å^3, $D_c = 1.032$ g cm^{-3}, space group $P\bar{1}$, $Z = 4$, μ(Mo-Kα) = 0.064 mm^{-1}. Data were collected on a Syntex-$P2_1$ diffractometer using graphite monochromated Mo-Kα radiation at room temperature. Reflections collected/unique 2122/1980, R(int) = 0.034. The structure was solved by direct methods (SHELXS86)[18] and refined by the full-matrix least-squares method (SHELXL93).[19] Final R and R_w values were 0.0847 and 0.1848 [1980 $I > 2\sigma(I)$ reflections]. Full crystallographic details, excluding structure factor tables, have been deposited at the Cambridge Crystallographic Data Centre (CCDC). CCDC reference number 207/363. See http://www.rsc.rsc.org/suppdata/p1/1999/3527/ for crystallographic data in .cif format.

Acknowledgements

We thank the analytical department of the Institute of Organic Synthesis for obtaining IR, GC and MS analyses.

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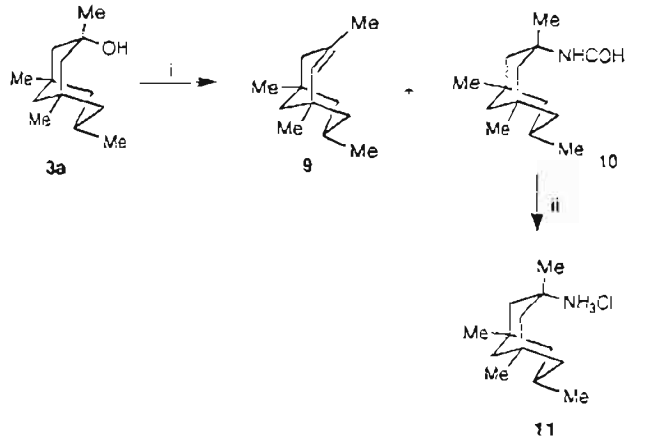
Table 1 Conversion of isomeric bicyclononanes **2** to tertiary alcohols **3** by organometallic reagents

Entry	Reaction conditions	Conversion to alcohols (%)[a] 3a	3b
1	MeMgI/Et_2O	50	9
2	MeLi/THF/cumene	70	40
3	MeMgI/$CeCl_3$/THF	100	100

[a] The conversion was determined from alcohol/ketone ratio by GC.

ciently.[9] 1,5,7-Trimethylbicyclononanones **2a** and **2b** displayed low to moderate conversion in reactions with methylmagnesium iodide and methyllithium, providing mixtures of the desired alcohols and starting ketones. Using the reagent prepared from methylmagnesium iodide and cerium trichloride, complete reaction was observed with both substances to give alcohols **3a** and **3b** in excellent yields (Table 1).

To introduce the amino group both alcohols **3a** and **3b** were used in the Ritter reaction with sulfuric acid and trimethylsilyl cyanide[10] as a hydrogen cyanide source (Scheme 3). Thus,



Scheme 3 *Reagents and conditions*: i, TMSCN, H_2SO_4, 34% of **9** and 55% of **10**; ii, H_3O^+, 71%.

1,3β,5,7α-tetramethylbicyclo[3.3.1]nonan-3α-ol **3a** gave 1,3,5,7β-tetramethylbicyclo[3.3.1]non-2-ene **9** and *N*-formyl-1,3,5,7-tetramethylbicyclo[3.3.1]nonan-3-amine **10** (34% of **9** and 55% of **10** by GC). The GC analysis of the reaction mixture indicated that only one amide isomer was formed. The other peaks registered with similar retention time were of negligible integral intensity (<1%). The ^1H NMR spectrum of the reaction product **10** was somewhat complicated due to the *cis–trans* isomerism of the formyl group, as could be seen from the different spin coupling constants of the formyl group protons. However, hydrolysis of formamide **10** undoubtedly gave one amine isomer **11** according to GC analysis, and ^1H and ^{13}C NMR spectra. As the correct stereochemical assignment of the formamido group could not be determined from simple ^1H NMR experiments due to the lack of any vicinal spin couplings, crystals of *N*-formyl derivative **10** were prepared for a single crystal X-ray analysis. This revealed two independent molecules (*a* and *b*) in the asymmetric unit cell (Fig. 1). These molecules differ in the orientation of the formylamino group. The torsion angles C5–C4–N3–C2 for the molecules *a* and *b* are −174.5(7) and 59.2(8)°, respectively. The bicyclo[3.3.1]nonane framework adopts a chair-boat conformation with the formamido group in the axial position of the chair.

There is little information in the literature about the stereochemistry of the Ritter reaction to explain the selective formation of **10**. Studies have been carried out only with 4-substituted cyclohexyl cations, showing the preference for axial nitrile

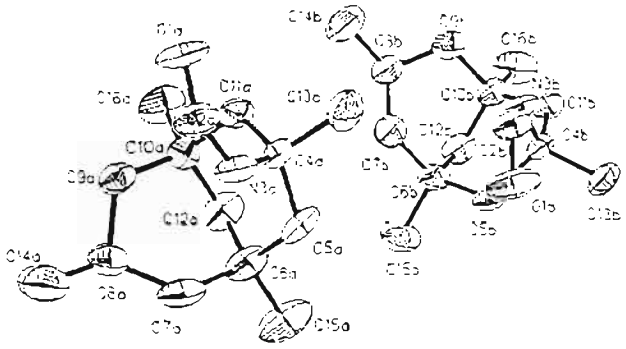


Fig. 1 Crystal structure of *N*-formyl-1,3,5,7β-tetramethylbicyclo-[3.3.1]nonan-3α-amine **10**.

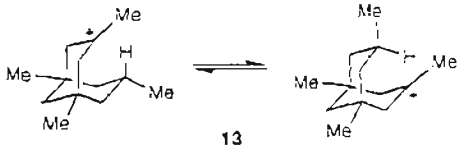
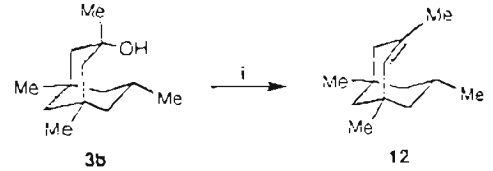


Fig. 2 Transannular hydride transfer in **13**.

attack.[11–13] Such a reaction course was explained by torsional strain caused by the 2,6-axial hydrogens, analogously to the nucleophilic addition to cyclohexanones.[11,12] Alternatively, Ichikawa suggested that the axial product resulted from the *trans*-antiparallel electrophilic addition of H^+ and CH_3CN to the olefinic bond.[13]

It is known that 3α-methylbicyclo[3.3.1]nonanone undergoes predominately *exo* attack of nucleophiles.[5] It is reasonable to assume that the capture of nitrile by the carbocation should also occur predominately from the *exo* face. Obviously, the selective *endo* product **10** formation cannot be explained by steric discrimination as the bicyclononyl cation should adopt the same conformation as the parent bicyclononanone. It is possible that *trans*-antiparallel addition as suggested by Ichikawa could be better rationalized as discrimination of the carbocation faces due to the differing C–C and C–H hyperconjugation.[14] The effect of hyperconjugation should thus override the steric factors. It is evident, however, that a more detailed investigation of the Ritter reaction stereochemistry should be carried out.

7β-Methylbicyclononanol **3b**, unlike its epimer **3a**, gave 1,3,5,7β-tetramethylbicyclo[3.3.1]non-2-ene **12** as sole product (93% by GC of the reaction mixture) and no formamide was isolated under the same Ritter reaction conditions (Scheme 4).



Scheme 4 *Reagents and conditions*: i, TMSCN, H_2SO_4, 66%.

It has been shown that the 7β-methylbicyclononan-3-yl cation **13** undergoes rapid transannular hydride transfer and exists in the double chair conformation (Fig. 2).[15] As a result of this, the *endo* face becomes inaccessible. The different reactivities of alcohols **3a** and **3b** provide additional evidence that amide formation from an obviously sterically unfavoured nitrile attack from the *endo* side of the carbocation is much more rapid than that from the *exo* side. This phenomenon requires an explanation which can be provided only on the basis of more extended studies. The results obtained for the Ritter reaction of both bicyclononanols **3a** and **3b** show that the stereoselectivity of

4. Pielikums

A Practical Synthesis of *tert*-Carbinamines via the Ritter Reaction with Chloroacetonitrile

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Abstract: Ritter reaction of tertiary alcohols with chloroacetonitrile and subsequent cleavage of chloroacetyl group with thiourea in resulting chloroacetamide is an efficient procedure for synthesis of *tert*-carbinamines.

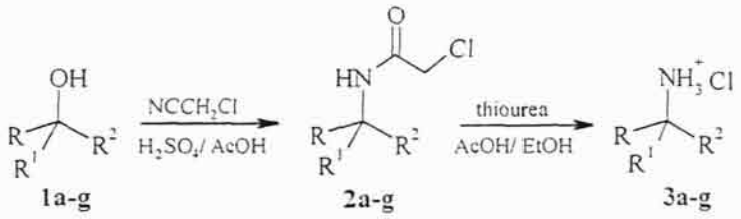
Key words: Ritter reaction, amines, amides, tertiary alcohols, cleavage

The reaction of nitriles or hydrogen cyanide with *in situ* generated carbocations giving *N-tert*-alkylamides (Ritter reaction[1]) is one of the few methods for introduction of the amino functionality at a tertiary carbon atom. Nevertheless the synthesis of *tert*-carbinamines via the Ritter reaction is limited to the use of the highly toxic hydrogen cyanide (HCN) because the formyl group in resulting formamide can be easily cleaved by either acidic or basic hydrolysis.[1b-d] In contrast to formamides, *N-tert*-alkylacetamides undergo retro-Ritter reaction during acidic hydrolysis[1a,2] and can be cleaved only by drastic alkaline hydrolysis[1a,1d] or by two step procedure involving *O*-alkylation of acetamide with triethyloxonium tetrafluoroborate.[3]

In connection with the development of a series of 1,3,5-alkylsubstituted cyclohexylamines acting as *N*-methyl-D-aspartate receptor antagonists,[4] we searched for a convenient approach toward *tert*-carbinamines avoiding the use of hazardous hydrazoic acid or HCN. We turned our attention to chloroacetamides as precursors of *tert*-alkylcarbinamines taking into account the smooth cleavage of the chloroacetyl

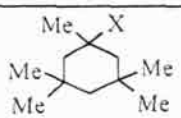
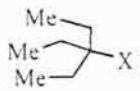
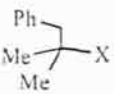
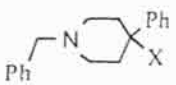
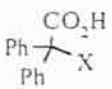
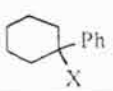
group with thiourea.[5] Synthesis of *N-tert*-alkylchloroacetamides by the Ritter reaction with chloroacetonitrile ($ClCH_2CN$) has already been reported.[1c] Herein we report an extension of this reaction to the synthesis of *tert*-carbinamines.

The Ritter reaction with $ClCH_2CN$ was carried out with structurally diverse tertiary alcohols **1a-g** (Scheme 1). Typically, high yields of chloroacetamides **2a-f** (Table 1) were obtained showing that amide formation with $ClCH_2CN$ is at least as efficient as with HCN or CH_3CN.[6]



Scheme 1

Table 1 Yields of chloroacetamides **2** and *tert*-carbinamines **3**

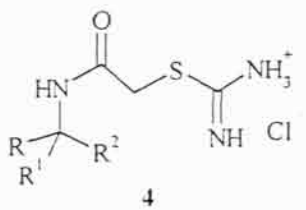
RR^1R^2CX	$X=NHCOCH_2Cl$ No., Yield (%)	$X=NH_3^+Cl^-$ No., Yield (%)
	**2a**, 86	**3a**, 89
	**2b**, 84	**3b**, 80
	**2c**, 95	**3c**, 85
	**2d**, 78	**3d**, 84
	**2e**, 73	**3e**, 74
	**2f**, 91	**3f**, 61
	**2g**,-	**3g**, -

*Isolated in the base form due to high hygroscopicity of dihydrochloride

In the case of 1-phenylcylohexanol **1g**, formation of amide **2g** was not observed: instead, 1-phenylcyclohexene was isolated as the major product. The poor ability of

cyclohexanol **1g** to form the corresponding amides in the Ritter reaction with PhCN and HCN has been reported previously and is apparently due to the low electrophilicity of the intermediate carbenium ion.[7] Noteworthy, 4-phenylpiperidin-4-ol **1e** reacts efficiently with CH_3CN,[8] and this was also found to be the case with $ClCH_2CN$.

Cleavage of the chloroacetyl group with thiourea was optimized using amide **2a** as an example. Conversion of amide **2a** to amine **3a** was monitored by TLC with isotiouronium salt **4**[5b,9] (Figure 2) as a reference standard (prepared alternatively). Noteworthy, the conversion was very slow when traditional reaction conditions e.g. boiling in neat ethanol were applied.[5a,b] Evidently, this could be attributed to the steric crowding in amides derived form *tert*-carbinamines when compared with the less branched secondary and tertiary amides.[5] It was observed, however, that the decomposition rate of **4** depends strongly on the concentration of acetic acid in the reaction mixture[5c,d] (Table 2).



4

Figure 1

Table 2 Optimization studies of chloroacetyl group cleavage in amide **2a**

Entry	EtOH/AcOH ratio	Disappearance of **4** (h)	Yield of **3a** (%)
1	20:1	18	81
2	10:1	11	85
3	5:1	7	88

Boiling of amide **2a** and thiourea in a mixture of ethanol and acetic acid (5:1) for 10 h were optimal and provided a high yield of amine **3a** (Table 1). These cleavage

conditions proved to be effective also in the case of chloroacetamides **2b-f** providing *tert*-carbinamines **3b-f** in good to excellent yields (Table 1).

In summary, it was demonstrated that the Ritter reaction with $ClCH_2CN$ and subsequent cleavage of the chloroacetyl group with thiourea is an efficient approach toward *tert*-alkylcarbinamines avoiding the use of the highly toxic hydrogen cyanide.

Acknowledgment

We acknowledge I. Dipans for obtaining IR spectra and E. Sarule for obtaining microanalyses. We also wish to thank Ph.D. A. Klapars for valuable comments during the preparation of the manuscript.

Experimental

Melting points were measured in capillary tubes on a Gallenkamp apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer 580B spectrometer. Microanalyses were performed on a Carlo Erba Instrument EA1108. ^1H and ^{13}C NMR spectra were determined on a Varian Mercury 200BB spectrometer with TMS as an internal standard. Preparative chromatography was carried out on Kieselgel 63-100 μm by flash column method.[10] TLC analysis was performed on Kieselgel 60 F_{254} plates (Merck). All chemicals were purchased from Aldrich. 1-Benzyl-4-hydroxy-4-phenylpiperidine **1e** was obtained by a known procedure.[8]

Chloroacetamides **2c**,[11] **2d**,[12] **2f**[13] and amines **3b**,[14] **3d**,[15] **3e**[8] are known. Amines **3c** and **3f** were identical with authentic samples obtained from Aldrich.

***N*-Chloroacetyl-*tert*-alkylamines 2a-f; General procedure**

To the alcohol **1** (5 mmol) and $ClCH_2CN$ (10 mmol) was added acetic acid (0.8 ml) and the mixture was cooled to 0-3 °C. Sulfuric acid (0.80 ml, 15 mmol) was added dropwise keeping the temperature below 10°C (in the case of alcohols **1d** and **1f** the amount of $ClCH_2CN$, acetic acid and sulfuric acid was tripled, otherwise the reaction

mixture was too thick to stir). The reaction mixture was allowed to reach room temperature, stirred for 5 h and poured into ice water (20 ml). Further workup procedure for individual amides was as follows.

Compounds **2a-c** formed a precipitate which was filtered off. The filter cake was washed with saturated aqueous $NaHCO_3$ (2×10 ml), H_2O (3×10 ml), dried *in vacuo* over NaOH, and purified by Kugelrohr short path distillation.

Compound **2d** was extracted with ether (3×20 ml). The combined extracts were washed with saturated aqueous Na_2CO_3 and brine and dried ($MgSO_4$) After solvent evaporation, the residue was purified by column chromatography eluting with 10% ethyl acetate in petroleum ether followed by 20% ethyl acetate in petroleum ether.

To isolate compound **2e**, the aqueous solution was made strongly basic with aqueous 20% NaOH. The resulting precipitate was collected on a filter, washed with H_2O (3×10 ml) followed by hexane (3×5 ml), and dried *in vacuo* over NaOH. Amide **2e** is stable in base form at room temperature for several months.

Compound **2f** formed precipitate which was collected on a filter and washed with H_2O (5×10 ml), then with ethanol (5 ml) and ether (3×5 ml) and dried *in vacuo* over NaOH.

***N*-Chloroacetyl-1,3,3,5,5-pentamethylcyclohexanamine (2a)**

Mp 86-88 °C. TLC (hexane/EtOAc, 6 : 1); R_f= 0.38.

IR (Nujol): ν_{max}= 3415, 3300, 1690, 1660 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 0.91 (6H, s), 1.07 (2H, d, J = 14 Hz), 1.14 (6H, s), 1.37 (3H, s), 1.0-1.45 (2H, m), 2.16 (2H, d, J = 14 Hz), 3.94 (2H, s), 6.4 (1H, br s).

^{13}C NMR (50 MHz, $CDCl_3$) δ= 28.70, 30.62, 32.18, 37.15, 43.95, 48.59, 52.23, 55.90, 165.70.

N-Chloroacetyl-3-ethylheptane-3-amine (2b)

Mp 56-57 °C. TLC (hexane/EtOAc, 6 : 1); R_f= 0.31.

IR (Nujol): ν_{max}=3270, 3080, 1685, 1660 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 0.81 (9H, t, J = 7 Hz), 1.73 (6H, d, J = 7 Hz), 3.97 (2H, s), 6.0 (1H, br s).

^{13}C NMR (50 MHz, $CDCl_3$) δ = 7.44, 26.36, 42.88, 60.14, 164.50.

N-Chloroacetyladamantane-1-amine (2c)

Mp 121-122 °C. TLC (hexane/EtOAc, 6 : 1); R_f= 0.30.

IR (Nujol): ν_{max}=3260, 3080, 1660 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ= 1.69 (6H, s), 2.03 (6H, s), 2.10 (3H, s), 3.94 (2H, s), 6.2 (1H, br s).

^{13}C NMR (50 MHz, $CDCl_3$) δ= 29.09, 36.10, 41.13, 42.81, 52.26, 67.40, 164.49.

N-Chloroacetyl-1,1-dimethyl-2-phenylethylamine (2d)

Mp 57-58 °C. TLC (hexane/EtOAc, 6 : 1); R_f= 0.30.

IR (Nujol): ν_{max}=3300, 1650 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ= 1.38 (6H, s), 3.03 (2H, s), 3.95 (2H, s), 6.2 (1H, br s), 7.1-7.4 (5H, m).

^{13}C NMR (50 MHz, $CDCl_3$) δ= 26.72, 42.90, 41.13, 44.99, 54.40, 126.47, 128.08, 130.30, 137.15, 165.09.

N-Benzyl-4-chloroacetamido-4-phenylpiperidine (2e)

Mp >135 °C (dec.). TLC (CH_3CN/H_2O/AcOH, 10 :1 : 0.3); R_f= 0.35.

IR (Nujol): ν_{max}=3280, 1665 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 2.0-2.4 (6H, m), 2.7-2.9 (2H, m), 3.55 (2H, s), 4.00 (2H, s), 6.75 (1H, s), 7.1-7.4 (10H, m).

^{13}C NMR (50 MHz, $CDCl_3$) δ = 35.43, 43.01, 49.39, 56.68, 63.06, 124.97, 127.0, 128.36, 129.08, 138.12, 144.82, 164.41.

_N_-Chloroacetyldiphenylglycine (2f)

Mp 213-214 °C (dec.). TLC ($CHCl_3$/MeOH/H_2O, 7 : 2 : 1 bottom layer); R_f= 0.15.

IR (Nujol): ν_{max}= 3340, 1710, 1640 cm^{-1}.

^1H NMR (200 MHz, DMSO-d_6): δ = 4.26 (2H, s), 7.1-7.4 (10H, m).

^{13}C NMR (50 MHz, DMSO-d_6) δ = 42.90, 69.91, 127.53, 127.91, 128.32, 140.45, 165.58, 171.89.

***tert*-Carbinamines 3a-f; General procedure**

A solution of amide **2** (5 mmol) and thiourea (0.46 g, 6 mmol) in a mixture of ethanol (10 ml) and acetic acid (2 ml) was refluxed for 10 h. The workup procedure for individual amines was as follows.

To isolate amines **3a-e**, water (50 ml) was added to the reaction mixture and the resulting precipitate was filtered. The filtrate was made alkaline with 20% NaOH. The product was extracted with hexane (3×30 ml), the combined extracts were washed with brine (30 ml) and dried over NaOH. The solution of amine in hexane was filtered through Celite pad, and 1.6 M HCl solution in ether (6 ml) was added. The solvent and the excess of HCl were removed *in vacuo*. The residue was treated with ethyl ether, filtered and dried over NaOH. Amine **3e** was isolated as a free base after evaporation of hexane.

To isolate amino acid **3f**, the reaction mixture was evaporated, and water (20 ml) was added to the residue. The resulting mixture was acidified to pH~1 and filtered. The filtrate was neutralized to pH 6-7 with 20% aqueous NaOH. The resulting precipitate was collected on a filter, washed with water (1ml) and dried *in vacuo* over NaOH.

1,3,3,5,5-Pentamethylcyclohexanamine hydrochloride (3a)

Mp 235 - 237°C. TLC (CH_3Cl/MeOH/25% aq.NH_3, 6 : 1 : 1 bottom layer); R_f= 0.50.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.02 (6H, s), 1.07 (6H, s), 1.23 (1H, d, J = 14 Hz), 1.30 (1H, d, J = 14 Hz), 1.64 (3H, s), 1.66 (2H, d, J = 14 Hz), 1.76 (2H, d, J = 14 Hz), 8.25 (3H, br s).

^{13}C NMR (50 MHz, $CDCl_3$) δ=28.19, 30.72, 32.41, 36.05, 48.43, 51.19, 57.53.

3-Ethylheptane-3-amine hydrochloride (3b)

Mp >280 °C. TLC ($CHCl_3$/MeOH/25% aq.NH_3, 6 : 1 : 1 bottom layer); R_f= 0.64.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.01 (9H, t, J = 7.5 Hz), 1.73 (6H, d, J = 7.5 Hz), 8.3 (3H, br s).

^{13}C NMR (50 MHz, $CDCl_3$) δ = 7.45, 28.03, 60.62.

Adamantane-1-amine hydrochloride (3c)

Mp >300°C. ($CHCl_3$/MeOH/25% aq.NH_3, 6 : 1 : 1 bottom layer); R_f=0.50.

^{1}H NMR (200 MHz, $CDCl_3$): δ= 1.68 (6H, s), 2.03 (6H, s), 2.14 (3H, s),

8.3 (3H, br s).

^{13}C NMR (50 MHz, $CDCl_3$) δ= 28.87, 35.30, 40.49, 52.87.

1,1-Dimethyl-2-phenylethylamine hydrochloride (3d)

Mp 196-200°C. TLC ($CHCl_3$/MeOH/25% aq.NH_3, 6 : 1 : 1 bottom layer); R_f= 0.68.

^{1}H NMR (200 MHz, $CDCl_3$): δ= 1.46 (6H, s), 3.09 (2H, s), 7.1-7.4 (5H, m),

8.5 (3H, br s).

^{13}C NMR (50 MHz, $CDCl_3$) δ= 25.07, 46.23, 55.77, 127.24, 128.44, 130.61, 134.68.

***N*-Benzyl-4-amino-4-phenylpiperidine (3e)**

Mp 60-61°C. TLC ($CHCl_3$/MeOH/25% aq.NH_3, 6 : 1 : 1 bottom layer); R_f= 0.78.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.48 (2H, br s), 1.70 (2H, d, J = 13 Hz) 2.1-2.3 (2H, m), 2.4-2.6 (2H, m), 2.70 (2H, dt, J = 14 Hz and 2 Hz), 3.56 (2H, s), 7.2-7.4 (8H, m), 7.45-7.6 (2H, m).

^{13}C NMR (50 MHz, $CDCl_3$) δ = 37.72, 49.78, 52.02, 63.14, 124.92, 126.41, 126.94, 128.14, 129.10, 138.54.

Diphenylglycine (3f)

Mp 245-247 °C (dec.) TLC (EtOAc/H_2O/n-BuOH/AcOH, 1 : 1 : 1 : 1); R_f= 0.74.

^1H NMR (200 MHz, D_2O): δ = 7.4-7.6 (m).

^{13}C NMR (50 MHz, D_2O) δ = 71.83, 130.28, 131.81, 132.53, 138.30, 174.11.

N-Aminoiminomethylthioacetyl-1,3,3,5,5-pentamethylcyclohexanamine hydrochloride (4)

A solution of amide **2a** (0.245 g, 1 mmol) and thiourea (0.092 g, 1.2 mmol) in ethanol (2 ml) was refluxed for 10 min. Ethanol was evaporated and the residue treated with acetonitrile (10 ml). The formed precipitate was collected by filtration and dried *in vacuo* to give **4** (0.120 g, 37%).

Mp 209 – 211° C, TLC ($CHCl_3$/MeOH/25% aq.NH_3, 6 : 1 : 1 bottom layer); R_f= 0.25.

IR (Nujol): ν_{max}= 3200, 3070, 1660 cm^{-1}.

^1H NMR (200 MHz, DMSO-d_6): δ = 0.86 (6H, s), 1.05 (6H, s), 1.20 (3H, s), 0.8 – 1.31 (4H, m), 2.18 (2H, d, J = 14 Hz), 3.93 (2H, s), 7.86 (1H, s), 8.34 (4H, br s).

^{13}C NMR (50 MHz, DMSO-d_6) δ=28.23, 29.95, 31.18, 34.62, 35.92, 46.48, 51.37, 54.64, 167.42, 170.36.

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(6) Alcohol **1a** in the Ritter reaction with HCN gave 85% of corresponding formamide, however, under the same conditions with CH_3CN the yield of acetamide was only 3% (Jirgensons, A.; Kauss, V. Unpublished results.)

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(9) Amide **2a** and thiourea quickly forms isothiouronium salt **4** which slowly decomposes to amine **3a**.

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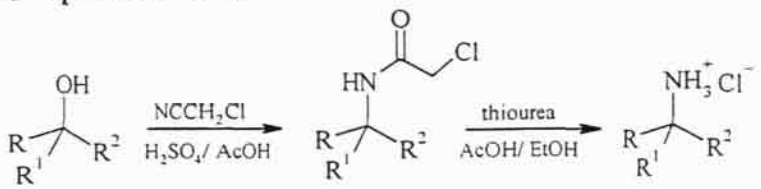
Graphic abstract



Elemental anaysis

***N*-Chloroacetyl-1,3,3,5,5-pentamethylcyclohexanamine (2a)**

Anal. Calcd for $C_{13}H_{24}ClNO$: C, 63.53; H, 9.84; N, 5.70. Found: C, 63.28; H, 9.94; N, 5.77.

***N*-Chloroacetyl-3-ethylheptane-3-amine (2b)**

Anal. Calcd for $C_9H_{18}ClNO$: C, 56.39; H, 9.46; N, 7.31. Found: C, 56.41; H, 9.62; N, 7.22.

***N*-Chloroacetyladamantane-1-amine (2c)**

Anal. Calcd for $C_{12}H_{18}ClNO$: C, 63.29; H, 7.97; N, 6.15. Found: C, 62.98; H, 8.02; N, 6.01.

***N*-Chloroacetyl-1,1-dimethyl-2-phenylethylamine (2d)**

Anal. Calcd for $C_{12}H_{16}ClNO$: C, 63.86; H, 7.14; N, 6.21. Found: C, 64.05; H, 7.19; N, 6.05.

***N*-Benzyl-4-chloroacetamido-4-phenylpiperidine (2e)**

Anal. Calcd for $C_{20}H_{23}ClN_2O$: C, 70.06; H, 6.76; N, 8.17. Found: C, 69.92; H, 6.75; N, 8.08.

***N*-Chloroacetyldiphenylglycine (2f)**

Anal. Calcd for $C_{16}H_{14}ClNO_3$: C, 63.27; H, 4.65; N, 4.61. Found: C, 62.90; H, 4.56; N, 4.45.

1,3,3,5,5-Pentamethylcyclohexanamine hydrochloride (3a)

Anal. Calcd for $C_{11}H_{23}N*HCl$: C, 64.21; H, 11.76; N, 6.81. Found: C, 63.74; H, 11.82; N, 6.48.

3-Ethylheptane-3-amine hydrochloride (3b)

Anal. Calcd for $C_7H_{18}N*HCl$: C, 55.43; H, 11.96; N, 9.23. Found: C, 55.41; H, 12.02; N, 9.05.

Adamantane-1-amine hydrochloride (3c)

Anal. Calcd for $C_{10}H_{17}N*HCl$: C, 63.99; H, 9.67; N, 7.46. Found: C, 63.62; H, 9.69; N. 7.29.

1,1-Dimethyl-2-phenylethylamine hydrochloride (3d)

Anal. Calcd for $C_{10}H_{15}N*HCl$: C, 64.68; H, 8.68; N, 7.54. Found: C, 64.43; H, 8.67; N, 7.35.

***N*-Benzyl-4-amino-4-phenylpiperidine (3e)**

Anal. Calcd for $C_{18}H_{22}N_2$: C, 81.16; H, 8.32; N, 10.52. Found: C, 81.15; H, 8.44; N, 10.36.

Diphenylglycine (3f)

Anal. Calcd for $C_{14}H_{13}NO_2$: C, 73.99; H, 5.77; N, 6.16. Found: C, 73.67; H, 5.63; N, 5.60.

N-Aminoiminomethylthioacetyl-1,3,3,5,5-pentamethylcyclohexanamine hydrochloride (4)

Anal. Calcd for $C_{14}H_{27}N_3OS*HCl*0.5H_2O$: C, 50.81; H, 8.83; N, 12.70; S, 9.69. Found: C, 50.93; H, 8.55; N, 12.63; S, 9.66.