Synthetic Entry to Tricyclic and Tetracyclic Quinuclidine Derivatives by Cycloaddition and Ring Transformation

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The (Z)-2-arylidene-quinuclidines **5 – 8** were synthesized. Their reaction with aliphatic dibasic functional reagents in both basic and acidic conditions afforded the fused heterocycles **9**, **10** and **11**. However, the reaction of arylidene derivative **5** with an aromatic dibasic functional reagent gave benzimidazole **13** in lieu of the anticipated tetracyclic system, quinuclidino[3,2-*e*]benzo[*b*]-1,4-diazepine **12**. Cycloadditions of **5** with different reagents gave the heterocyclic derivatives **17**, **19**, **22** and **23**. Acid-catalyzed cyclization of **5** with excess resorcinol gave **24**. Compounds **9a**, **19** and **24** showed antibacterial activities.

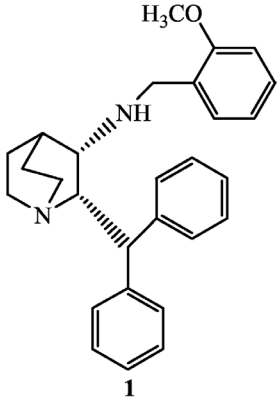
Key words: Quinuclidine, Annulation, Dibasic Functional Reagent, Antibacterial Activity

Introduction

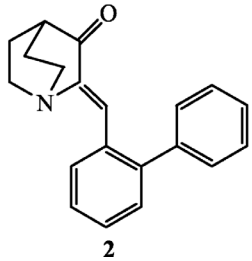
The non-peptide substance P antagonist CP-96,345 **(1)** was the first potent and selective NK-1 receptor antagonist, which has effects in animal models of pain and inflammation [1 – 4]. Structure activity relationship (SAR) studies on **1** have mainly focused on variations of the benzylamine moiety at C-3 position [5, 6] and modification in the C-2 position, as exemplified In by 2-(2-phenylbenzylidene)-1-azabicyclo[2.2.2]octan-3-one (**2**) [3, 7] and 1-azabicyclo[2.2.2]octane-2-spirocyclopropane derivative **3** [8]. In view of the aforementioned information, it seemed of interest to design and synthesize new quinuclidine derivatives which incorporate heterocyclic moieties of biological value. In the course of the present investigation we have synthesized a number of novel 1-aza-bicyclo[2.2.2]octane derivatives with modifications in the C-2 position as the 2-substituted benzylidene-3-quinuclidinones **5 – 8** which can be used as precursors for the synthesis of various heterocycle-annulated quinuclidine (1-azabicyclo[2.2.2]octane) derivatives.

Results and Discussion

Several arylidene derivatives have bacteriostatic as well as strong fungistatic action [9]. Therefore, compounds **5 – 8** were synthesized according to our modification to the method of Warawa and Campbell [10]. Claisen-Schmidt condensation of 1-aza-bicyclo[2.2.2]octan-3-one hydrochloride (**4**) with appropriate aldehydes, namely, benzaldehyde [10],



1



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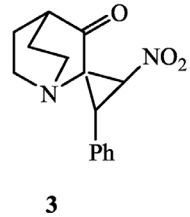

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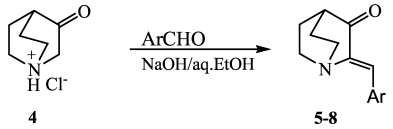
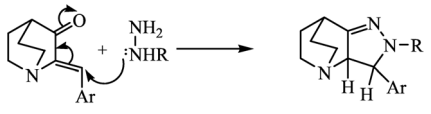


4 **5-8**

Ar : C_6H_5 (**5**); 4-$C_6H_4N(Me)_2$ (**6**); 3,4-$(OCH_2O)C_6H_3$ (**7**); 2-Thienyl (**8**)



9,10

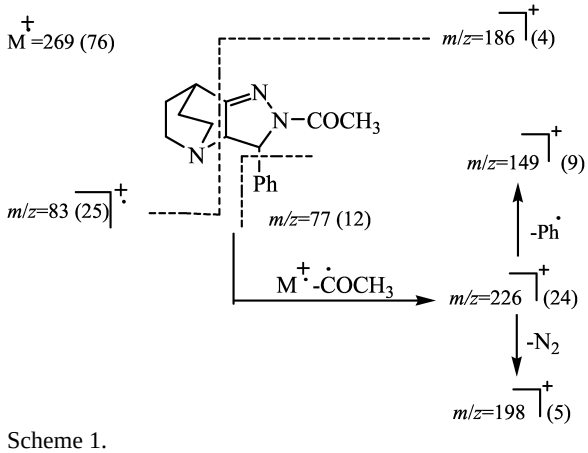
9a: Ar = C_6H_5, R = H; **9b**: Ar = C_6H_5, R = C_6H_5; **10a**: Ar = C_6H_5, R = $COCH_3$; **10b**: Ar = 3,4-$(OCH_2O)C_6H_3$, R = $COCH_3$

4(*N*,*N*-dimethylamino)benzaldehyde, piperonal and thiophene-2-carboxaldehyde in the presence of aqueous alcohol and sodium hydroxide gave a single isomer of the corresponding (*Z*)-2-arylidenes **5 – 8**. Their structures were confirmed by ^{1}H NMR spectra which showed the olefinic proton at $\delta = 7.8$ ppm and the lowering of the stretching frequency of the C=O group in the IR spectra from 1740 to 1690 cm^{-1} due to formation of α,β-unsaturated ketones. In addition, mass spectra gave the expected molecular ion peak as the base peak for **6 – 8**.

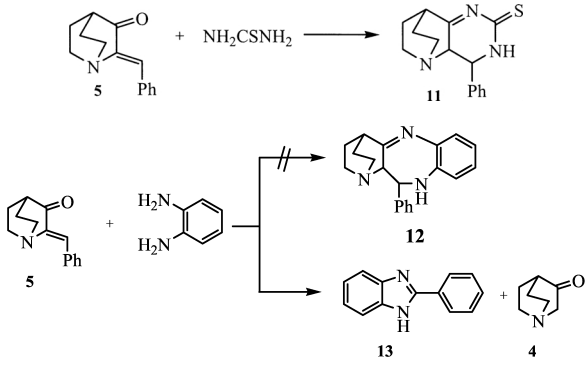
Pyrazolines have been shown to be useful in the area of chemotherapy [11 – 13]. Therefore, attachment of a pyrazoline moiety on a quinuclidine ring at 2, 3-positions is of special interest since both moieties possess pharmacological activity. Thus, (*Z*)-2-arylidene-1-azabicyclo[2.2.2]octan-3-ones **5** and **7** were used as precursors for the synthesis of tricyclic quinuclidino[3,2-*c*]pyrazolines, *via* Michael condensation through their reaction with hydrazine derivatives as dibasic functional reagent, whereby the nucleophile attacks the carbonyl carbon rather than β-carbon of the olefinic bond.

Condensation of **5** with hydrazine hydrate or phenylhydrazine in sodium methoxide gave the quinuclidinopyrazolines **9a**, **b**, respectively. Treatment of **5** and **7** with hydrazine hydrate in glacial acetic acid afforded the corresponding *N*-acetylpyrazolines **10a**, **b**.

Formulations of structures **9a, b** and **10a, b** are based on elemental analysis, IR, ^{1}H NMR and mass spectral data. The ^{1}H NMR spectrum of **9b** shows a doublet signal of N-methine at $\delta = 3.9$, a doublet signal of phenylmethine at 4.8 and a multiplet of aromatic protons at 6.8 – 7.5 ppm. Additionally the mass spectral fragmentation pattern of **9a** and **10a, b** is in agreement with their structures. The fragmentation pattern of **10a** is depicted in Scheme 1.

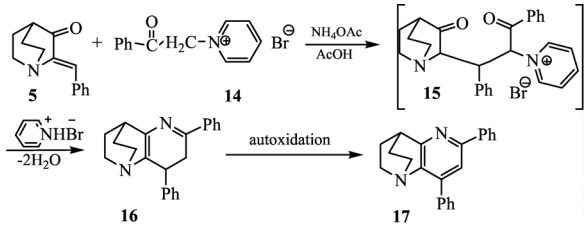


Scheme 1.



Furthermore, 2-thiopyrimidine derivatives were found to be useful agents as antithyroids [14] and in pesticides [15]. Therefore, building a thiopyrimidine moiety on a quinuclidine ring is of interest since both moieties possess pharmacological activity. Thus, the reaction of 2-benzylidene-1-azabicyclo[2.2.2]octan-3-one **(5)** with thiourea in the presence of sodium methoxide gave the expected quinuclidino[3,2-*d*]pyrimidine-2-thione **11**. Its structure was ascertained by elemental analysis, IR, ^{1}H NMR and MS data. Its ^{1}H NMR spectrum revealed the presence of a (singlet) signal for the secondary amine at $\delta = 3.37$, a (doublet) signal for N-methine at 4.32 and a (triplet) signal for phenyl-methine at 4.8. In addition its mass spectrum gave a molecular ion peak $(m/z = 271)$ as the base peak.

On the other hand, the reaction of the aromatic dibasic reagent *o*-phenylenediamine with compound **5**, to synthesize the tetracyclic system quinuclidino[3,2-*e*]benzo[*b*]-1,4-diazepine **12**, was unsuccess-

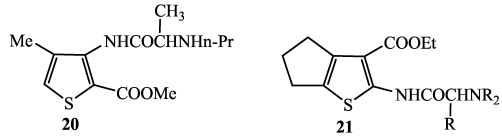


Scheme 2.

ful. Instead 2-phenylbenzimidazole (**13**) was unequivocally obtained. The constitution of **13** was proved by its identical melting point with that reported in the literature [16] besides its IR, ^{1}H NMR and MS spectra. The formation of benzimidazole **13** is in accordance with the mechanistic proposal given by Zoorob *et al.* [17] and Tanaka *et al.* [18].

Recent studies have provided an efficient method for the synthesis of various fused heterocyclic compounds containing the dihydropyridine moiety [19 – 21]. Since 1,4-dihydropyridine systems show exceptional properties as calcium antagonists [22], as powerful arteriolar vasodilators [23] and also as inhibitors of dihydrofolate reductase [24, 25], we decided to synthesize the quinuclidino[3,2-*b*]dihydropyridine **16** by treatment of pyridinium salt **14** with ammonium acetate in glacial acetic acid and **5** to give the 1,5-diketone **15** *via* a Michael type addition. The diketone **15** undergoes ring closure on treatment with ammonium acetate to give the pyrido-annulated quinuclidine **17**, *via* autooxidation of intermediate **16**, as shown in Scheme 2.

Annulation of **17** with an uracil moiety fused to C^2-C^3 of the pyridine ring was achieved through alkylation of 6-amino-1,3-dimethyluracil (**18**) with **5**. The alkylation of enamines with electrophilic olefins has become one of the most efficient methods of alkylation of carbonyl compounds [26]. The problem of C- and N-alkylation of enamines has been investigated



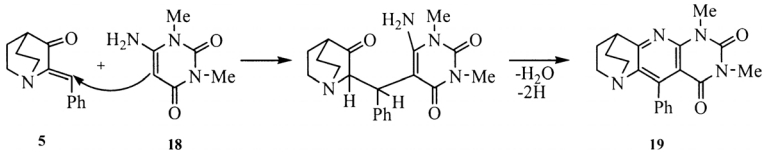
by Troschutz and Ander [27] who revealed that the β-carbon center is more nucleophilic than the amino group. No attention has been paid to the similar reaction with **18**, which can be used as a key intermediate for the building of a pyridopyrimidine moiety fused with the quinuclidine ring. The reaction of **5** with uracil **18** in presence of glacial acetic acid gave the pyrido[2,3-*d*]pyrimidine adduct **19** (Scheme 3). Its structure was confirmed by elemental analysis, IR, ^{1}H NMR and MS spectra. The mass spectrum gave a molecular ion peak as a base peak ($m/z = 348$), and the MS fragmentation pattern of **19** agreed with the proposed structure.

Moreover carticaine **20** [28 – 31] and carticaine analogues **21** [32] were proved to be local anesthetics and antiarrhythmic agents. The thiophene ring of carticaine was replaced by the quinuclidine moiety to prepare a carticaine analogue in an attempt to increase its biological activity.

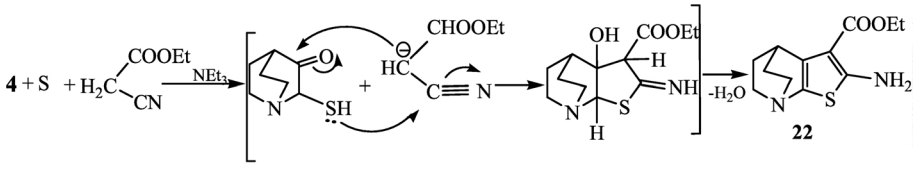
Therefore the synthesis of the target compound **22** was prepared according to the Gewald method [33] by reaction of compound **4** with ethyl cyanoacetate and sulphur in the presence of triethylamine. The reaction mechanism for the formation of **22** can be lucidly explained as illustrated in Scheme 4.

The analytical and spectral data are consistent with the proposed constitution **22**. The mass fragmentation pattern of **22** agrees with the proposed structure as shown in Scheme 5.

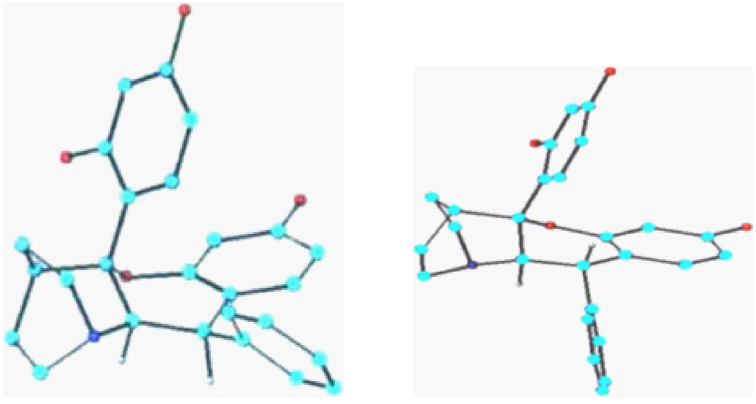
A one-step synthesis of quinuclidino[3,2-*b*]thiophene derivative **23** was conducted in high yield. The reaction of 2-benzylidene-3-quinuclidinone (**5**) with



Scheme 3.

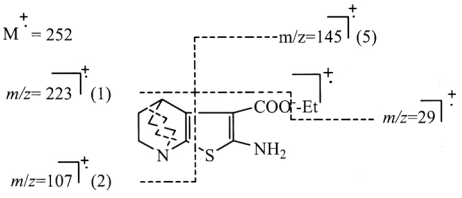


Scheme 4.

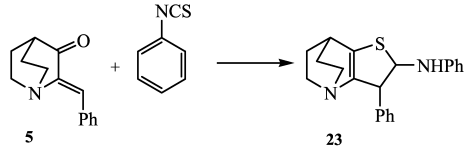


cis-Configuration *trans-Configuration*

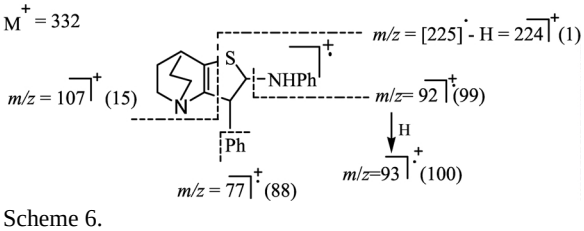
Fig. 1. Molecular modeling for *cis*- and *trans*-configuration of **24** obtained from PM3 semi-empirical MO geometry optimization.



Scheme 5.



5 **23**

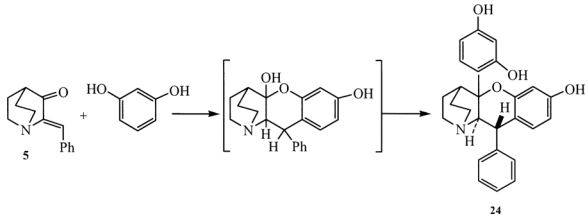


Scheme 6.

phenylisothiocyanate afforded this product, the structure of which was established on the basis of analytical and spectral data. The main characteristic feature of its IR spectrum are absorptions indicative of NH (3216 cm^{-1}) and C-S (1087) stretching vibrations.

The mass spectrum of **23** gave a molecular ion peak at $m/z = 332$ and intense peaks at 77 (88%) and 92 (98%) corresponding to the splitting of the phenyl and phenylamino fragments. The base peak at $m/z = 93$ (100%) is due to ($PhNH^{+\bullet} + H^{\bullet}$) as shown in Scheme 6.

A few reports have been cited in the literature for the acid-catalyzed reaction of resorcinol with α,β-unsaturated ketones, in particular with mesityl oxide [34 – 37]. Recently, Livant [38] reported the reaction of excess resorcinol with α,β-unsaturated ketones giving a single clean product in good yield. Therefore, we decided to investigate the acid-catalyzed cyclization of **5** with excess resorcinol whereby **24** was isolated in 72% yield.



24

Its constitution was supported by elemental analysis, IR, ^{1}H NMR and MS spectra. The ^{1}H NMR spectrum of **26** not only confirms the constitution, but also indicates the stereochemistry of this compound. The large coupling of 10 Hz between 9-H and 9a-H suggested the trans configuration of 9-H and 9a-H in this compound the quantum mechanical semi-empirical molecular orbital method PM3 was used to optimize the geometry of the molecule. The trans configuration was found to have the lower total energy (−6164.73 kcal/mol), whereas the cis configuration was found to have a total energy of (−6150.30 kcal/mol). This indicates the global stability of the trans configuration (see Fig. 1).

Biological Activity

The antibacterial activity was evaluated by using the agar plate method. In this method two bacterial strains namely Escherichia coli (Gram negative) and Bacillus subtilis (Gram positive) were used as test organ-

Table 1. Diameter of inhibition zone in mm as a criterion of antibacterial activity of some synthesized quinuclidine derivatives at a concentration of 100 ppm.

Comp.	Bacteria			
	E. coli		B. subtilis	
	Action	Zone (mm)	Action	Zone (mm)
5	–	–	–	–
7	–	–	–	–
9a	+	24	+	11
11	–	–	–	–
21	+	2	+	13
26	+	4	+	7
$CHCl_3$	–	–	–	–
DMSO	–	–	–	–

isms. Agar nutrient medium was prepared, autoclaved and poured into sterilized Petri dishes. Few drops of dense bacterial suspension were gently spread over the medium surface using a sterilized spatula. The bacterial smear was left to dry and then, a number of pores were made on agar-nutrient medium using a sterilized corck porer. For screening the antibacterial activities, solutions of the tested compounds (100 ppm) were transferred separately into the pores without overflow. The tested compounds were dissolved in $CHCl_3$, or DMSO. Therefore, $CHCl_3$ and DMSO were included as references for comparison. The test was carried out under completely aseptic conditions. The plates were then incuabated at 32 ± 2 °C for 24 h. The antibacterial activity was expressed as the diameter (mm) of inhibition zone.

The results of antibacterial activities of some synthesized quinuclidine derivatives are shown in Table 1. Test solutions of these compounds were tested at a concentration level of 100 ppm. It should be mentioned that both $CHCl_3$ and DMSO did not show any inhibition on bacterial growth.

Based on the diameter of inhibition zones, the antibacterial activity of the tested compound on the growth of *E. coli* can be ranked descendingly as compounds **9a** > **26** > **21**. This order was changed in case of *B. subtil*is to be **21** > **9a** > **26**. The rest of the tested compounds showed no antibacterial activity. This finding may suggest the possible use of the compounds that showed antibacterial activity in the field of chemotherapy as antibacterial agents.

Experimental Section

All melting points (uncorrected) were determined on a Gallenkamp electric melting point apparatus. Elemental microanalyses were carried out at Microanalytical Unit, Faculty of Science, Cairo University. Infrared spectra were measured on a Mattson 5000 FTIR spectrometer. ^{1}H NMR data were obtained in $CDCl_3$ or DMSO solution on a Varian XL 200 MHz instrument using TMS as internal standard. Chemical shifts were reported in ppm (δ) downfield from internal TMS. Mass spectra were recorded on a GC-MS QP-1000 EX Shimadzu instrument. Microbiological screening was carried out at the Botany Department, Faculty of Science, Mansoura University. Reactions were monitored by thin layer chromatography (TLC) using EM science silica gel coated plates with visualization by irradiation with ultraviolet lamp.

2-Arylidene-1-azabicyclo [2.2.2] octan-3-ones **5 – 8**

General procedure: Compound **4** (1 g, 6 mmol) and 4 pellets of NaOH (0.4 g) were completely dissolved in 3 ml of H_2O, then 4 ml of ethanol and the appropriate aldehyde (6 mmol) was added. The reaction mixture was refluxed for 30 min and left to cool. Yellow crystals were separated, filtered off, washed with aqueous EtOH and crystallized from MeOH to give the desired arylidene compounds **5 – 8**.

*2-Benzylidene-1-azabicyclo [2.2.2] octan-3-one (***5***)*

M. p. 131 – 133 °C (methanol) (lit. [10]: m. p. = 133 °C). – R_f = 0.91 (pet. ether 40 – 60 °C/ethyl acetate, (1:1)). – Yield 90% (yellow crystals). – IR (KBr): $\tilde{\nu}$ = 1621 (C=C), 1702 cm^{-1} (α,β-unsaturated CO). – $C_{14}H_{15}NO$ (213.3): calcd. C 78.84, H 7.09, N 6.57; found C 78.67, H 7.05, N 6.48.

*2-(4-Dimethylaminobenzylidene)-1-azabicyclo [2.2.2] octan-3-one (***6***)*

M. p. 60 °C (methanol) – Yield 92.8% (yellow crystals). – IR (KBr): $\tilde{\nu}$ = 1623 (C=C), 1698 cm^{-1} (α,β-unsaturated CO). – MS (EI, 70 eV): *m/z* (%) = 257 (20) [M^++1], 256 (100, base peak) [M^+], 213 (12) [M^+-N (CH_3)$_2$]. – $C_{16}H_{20}N_2O$ (256.34): calcd. C 74.96, H 7.86, N 10.93; found C 74.85, H 7.77, N 10.82.

*2-(Benzo[1,3]dioxol-4-ylmethylene)-1-azabicyclo [2.2.2] octan-3-one (***7***)*

M. p. 178 °C (methanol) – Yield 71% (yellow crystals). – IR (KBr): $\tilde{\nu}$ = 1613 (C=C), 1692 cm^{-1} (α,β-unsaturated CO). – ^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.0 (m, 4H, (CH_2)$_2$-C), 2.6 (q, 1H, *bridgehead*), 3.0 (m, 4H, (CH_2)$_2$-N), 5.9 (s, 2H, O-CH_2-O), 6.5 – 7.2 (m, 3H, *aromatic*), 7.8 (s,1 H, =C*H*). – MS (EI, 70 eV): *m/z* (%) = 258 (17) [$M^+ + 1$], 257 (100, base peak) [M^+] 256 (9) [$M^+ - 1$], 135 (17) [M^+ -$C_7H_5O_2$]. – $C_{15}H_{15}NO_3$ (257.28): calcd. C 70.02, H 5.88, N 5.44; found C 69.94, H 5.81, N 5.33.

*2-(Thiophen-2-ylmethylene)-1-azabicyclo [2.2.2] octan-3-one (**8**)*

M. p. 112 °C (methanol) – Yield 83.7% (yellow crystals). – IR (KBr): $\tilde{\nu} = 1615$ (C=C), 1694 cm^{-1} (α,β-unsaturated CO). – MS (EI, 70 eV): *m/z* (%) = 221 (6) [M$^+ + 2$], 220 (14) [M$^+ + 1$], 219 (100, base peak) [M$^+$], 135 (26) [M$^+$ -thienyl]. – $C_{12}H_{13}$ NOS (219.29): calcd. C 65.72, H 5.97 , N 6.42; found C 65.88, H 5.86, N 6.61.

3-Phenyl-4-substituted-1,4,5-triazatricyclo[5.2.2.0^{2,6}]-undec-5-enes **9a**, **b**

General procedure: A mixture of **5** (0.5 g, 2 mmol) and NH_2NHR (2 mmol) in 3 ml of methanol and NaOMe-MeOH (0.046 g Na, 2 mmol, in 10 ml MeOH) was refluxed for 8 h. The reaction mixture was cooled then poured into cooled water, the deposite solid was filtered off, washed with water and purified using preparative chromatography on Al_2O_3 (pet. ether 40 – 60 °C/ethyl acetate (2:8) as eluent) to give **9a**, **b**.

*3-Phenyl-1,4,5-triazatricyclo[5.2.2.0^{2,6}]undec-5-ene (**9a**)*

M. p. 65 °C – Yield 55% – $R_f = 0.34$ (pet. ether 40 – 60 °C/ethyl acetate (2:8)). – IR (KBr): $\tilde{\nu} = 1463$ (C=N), 3188 cm^{-1} (NH) – ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 1.8$ (m, 4 H, (C*H*$_2$)$_2$C), 2.6 (q, H, *bridgehead*), 2.9 (m, 4 H, (C*H*$_2$)$_2$N), 4.3 (d, $J = 1.2$ Hz, 1 H, C-C*H*-N), 4.4 (d, $J = 1.3$ Hz, 1 H, Ph-C*H*-NH), 6.4 (s, 1 H, N*H*), 7.2 – 7.8 (m, 5 H, *arom.*) – MS (EI, 70 eV): *m/z* (%) = 227 (22), [M$^+$], 171 (100, base peak), 150 (8) [M$^+$-Ph], 122 (9) [M$^+$-PhN]. – $C_{14}H_{17}N_3$ (227): calcd. C 73.97, H 7.54, N 18.49; found C 73.83, H 7.45, N 18.31.

*3,4-Diphenyl-1,4,5-triazatricyclo[5.2.2.0^{2,6}]undec-5-ene (**9b**)*

M. p. 195 °C – Yield 69.3%. – $R_f = 0.63$ (pet. ether 40 – 60 °C/ethyl acetate (2:8)). IR (KBr): $\tilde{\nu} = 1468$ cm^{-1} (C=N). – ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 1.8$ (m, 4 H, (C*H*$_2$)$_2$C), 2.9 (q, 1 H, *bridgehead*), 3.05 (m, 4 H, (C*H*$_2$)$_2$N), 3.85 (d, $J = 1.7$ Hz, 1 H, C*H*-N), 4.8 (d, $J = 1.8$ Hz, 1 H, N-C*H*-Ph), 6.8 – 7.5 (m, 10 H, *arom.*). – $C_{20}H_{21}N_3$ (303.39): calcd. C 79.17, H 6.98, N 13.85; found: C 79.03, H 6.87, N 13.74.

*1-(3-Aryl-1,4,5-triazatricyclo[5.2.2.0^{2,6}]undec-5-en-4-yl)-ethanones (**10a**, **b**)*

General procedure: A mixture of **5** or **7** (2 mmol) and hydrazine hydrate (0.116 ml, 2 mmol) was refluxed for 8 h in glacial acetic acid. Basification of the cold reaction mixture was achieved with 50% NaOH, and the formed precipitate was filtered off, dried and purified using preparative chromatography on Al_2O_3 (pet. ether 40 – 60 °C/ethyl acetate (2:8) as eluent) to give **10a**, **b**.

*1-(3-Phenyl-1,4,5-triazatricyclo[5.2.2.0^{2,6}]undec-5-en-4-yl)-ethanone (**10a**)*

M. p. 126 °C – Yield 59.5%. – $R_f = 0.73$ (pet. ether 40 – 60 °C/ethyl acetate (2:8)). – IR (KBr: $\tilde{\nu} = 1434$ (C=N), 1653 cm^{-1} (N-CO-CH_3). – ^{1}H NMR (200 MHz $CDCl_3$) $\delta = 1.2$ (s, 3 H, C*H*$_3$-CO), 1.8 (m, 4 H, (C*H*$_2$)$_2$C), 2.6 (q, 1 H, *bridgehead*), 3.0 (m, 4 H, (C*H*$_2$)$_2$N), 4.2 ([d, $J = 2$ Hz, 1 H, C-C*H*-N), 4.6 ([d, $J = 2$ Hz, 1 H, N-C*H*-Ph), 7.1 – 7.9 (m, 5 H, *arom.*). – MS (EI, 70 eV): *m/z* (%) = 270 (14) [M$^+ + 1$], 269 (76) [M], 226 (24) [M$^+$-$COCH_3$], 144 (100, base peak). – $C_{16}H_{19}N_3O$ (269.33): calcd. C 71.35, H 7.11, N 15.60; found C 71.43, H 7.02, N 15.44.

*1-[3-(Benzo[1,3]dioxol-4-yl)-1,4,5-triazabicyclo-[5.2.2.0^{2,6}]undec-5-en-4-yl]-ethanone (**10b**)*

M. p. 60 °C – Yield 46%. – $R_f = 0.53$ (pet. ether 40 – 60 °C/ethyl acetate (2:8)). – IR (KBr): $\tilde{\nu} = 1444$ (C=N), 1657 cm^{-1} (N-CO-CH_3). – MS (EI, 70 eV): *m/z* (%) = 313 (75) [M$^+$, 270] (62) [M$^+$-$COCH_3$], 188 (100, base peak). – $C_{17}H_{19}N_3O_3$ (313.34): calcd. C 65.16, H 6.11, N 13.41; found C 65.24, H 6.32 N, 13.34.

*3-Phenyl-1,4,6-triaztricyclo[6.2.2.0^{2,7}]dodec-6-ene-5-thione (**11**)*

The arylidene **5** (0.5 g, 2 mmol) and thiourea (0.152 g, 2 mmol) were refluxed in NaOMe-MeOH (0.046 g Na, 2 mmol, in 10 ml MeOH) for 2 h. The formed precipitate was washed with $CHCl_3$ (2×10 ml) to dissolve the excess arylidenes to yield 0.42 g of a white precipitate, which was recrystallized from ethanol to afford **11**. M. p. 210 °C. – Yield 77.5% (white crystals). – IR (KBr): $\tilde{\nu} = 1455$ (C=N), 1562 (C=S), 3169 cm^{-1} (NH). – ^{1}H NMR (200 MHz, [D_6]-DMSO): $\delta = 1.67$ (m, 4 H, (C*H*$_2$)$_2$C), 3.01 (q, 1 H, *bridgehead*), 3.05 (m, 4 H, (C*H*$_2$)$_2$N), 3.37 (s, 1 H, N*H*), 4.3 (d, $J = 1.2$ Hz, 1 H, N-C*H*-C), 4.8 (d, $J = .8$ Hz, 1 H, N-C*H*-Ph), 7.24 – 7.37 (m, 5 H, *arom.*). – MS (EI, 70 eV): *m/z* (%) = 271 (100, base peak) [M$^+$], 256 (16) [M$^+$-CH_2], 242 (24) [M$^+$ -2CH_2], 194 (45), 149 (24) [M$^+$-Ph]. – $C_{15}H_{17}N_3S$ (271.38): calcd. C 66.38, H 6.32, N 15.48; found C 66.42, H 6.23, N 15.53.

Reaction of the arylidene **5** *with o-phenylenediamine; formation of 2-phenylbenzimid-azole (**13**)*

A mixture of **5** (0.5 g, 2 mmol) and *o*-phenylenediamine (0.22 g, 2 mmol) was refluxed in glacial acetic acid for 5 h. The reaction mixture was cooled and poured into ice water, extracted with ethyl acetate (3×15 ml) to give a mixture of two products which were identified as compounds

4 and **13** by TLC (pet. ether 40 – 60 °C/ethyl acetate (1:1)) having $R_f = 0.01$ and 0.61, respectively. 2-Phenylbenzimidazole (**13**) was separated by preparative chromatography on Al_2O_3 using the same eluent (identical to that reported in literature [16]). – **13**: M. p. 283 °C (lit. [16]: m. p. 285 °C). – $R_f = 0.61$ (pet. ether 40 – 60 °C/ethyl acetate (1:1)). – IR (KBr): $\tilde{\nu} = 1600$ (C=C), 3200 cm^{-1} (NH). – ^1H NMR (200 MHz, $CDCl_3$): $\delta = 7.2 - 8.19$ (m, 9H, *arom.*), 12.9 (s, 1H, N*H*). – MS 194 (100, base peak) [M^+].

*3,5-Diphenyl-1,6-diaza-tricyclo[6.2.2.0^{2,7}]dodeca-2(7),3,5-triene (**17**)*

Compound **5** (1 g, 5 mmol) was added to a mixture of phenacyl bromide (0.9 g, 5 mmol) and pyridine (0.4 ml, 5 mmol). Then ammonium acetate (4 g) in glacial acetic acid was added and the reaction mixture was refluxed for 10 min to give a brownish precipitate which was filtered off, washed with ice water and dried to give 1.5 g of compound **17** which crystallized from absolute ethanol. – M. p. 204 °C (ethanol). – Yield 95%. – IR (KBr): $\tilde{\nu} = 1600$ (C=C), 2956 cm^{-1} (aliphatic C-H). – ^1H NMR (200 MHz, $CDCl_3$): $\delta = 1.9$ (m, 4 H, (CH_2)$_3$C), 2.6 (q, 1 H, *bridgehead*), 3.2 (m, 4 H, (CH_2)$_2$N), 7.2 – 8.03 (m, 11 H, *arom.*) – MS (EI, 70 eV): *m/z* (%) = 312 (100, base peak) [M^+], 283 (68) [M^+-2CH_2]. – $C_{22}H_{20}N_2$ (312.4): calcd. C 84.58, H 6.45, N 8.97; found C 84.64, H 6.38, N 8.82.

*1,3-Dimethyl-10-phenyl-5,6,7,8-tetrahydro(1H)-1,3,5,9-tetraza-5,8-ethanoanthracene-2,4-dione (**19**)*

A solution of compound **5** (1 g, 5 mmol) and 6-amino-1,3-dimethyl uracil (0.63 g, 5 mmol) in glacial acetic acid was refluxed for 15 h. The reaction mixture was cooled, then poured into ice water and basified with ammonia solution to yield 0.87 g of **19** as a yellow precipitate. Purification was achieved by preparative chromatography on Al_2O_3 using pet. ether 40 – 60 °C/ethyl acetate (1:1) as eluent. – M.p. 290 °C. – Yield 62.5%. – $R_f = 0.54$ (pet. ether 40 – 60 °C/ethyl acetate (1:1)). – IR (KBr): $\tilde{\nu} = 1708$ (NCOC), 1764 cm^{-1} (N-CO-N). – ^1H NMR ($CDCl_3$): $\delta = 1.9$ (m, 4 H, (CH_2)$_2$C), 2.6 (q, 1 H, *bridgehead*), 2.9 (m, 4 H, (CH_2)$_2$N), 3.3 (s, 3 H, C-NCH_3-CO), 3.8 (s, 3 H, CO-NCH_3CO), 7.1 – 7.4 (m, 5 H, *arom.*). – MS (EI, 70 eV): *m/z* (%) = 348 (100, base peak) [M^+], 319 (73) [M^+-2 Me]. – $C_{20}H_{20}N_4O_2$ (348.39): calcd. C 68.95, H 5.79, N 16.08; found C 68.71, H 5.63, N 16.21.

*4-Amino-1-aza-3-thia-tricyclo[5.2.2.0^{2,6}]undeca-2(6),4-diene-5-carboxylic acid ethyl ester (**22**)*

A solution of compound **4** (0.8 g, 5 mmol) was heated with triethylamine (10 mmol) for 2 h in ethanol, then ethyl cyanoacetate (0.57 ml, 5 mmol) and sulphur (0.16 g, 5 mmol) were added to the reaction mixture. The reaction mixture was heated on a water bath for 5 h. It was poured onto acidic cold water to give a yellow precipitate which was filtered off, washed with water and dried to give 0.35 g of compound **22**. It was purified by preparative chromatography on Al_2O_3 using pet. ether 40 – 60 °C/ethyl acetate (1:1) as eluent. – M. p. 115 °C – Yield 28%. – $R_f = 0.67$ (pet. ether 40 – 60 °C/ethyl acetate (1:1)). – IR (KBr): $\tilde{\nu} = 1723$ (CO of ester), 3427 cm^{-1} (NH_2). – ^1H NMR (200 MHz, $CDCl_3$): $\delta = 1.3$ (t, $J = 1.4, .8$ Hz, 3 H, CH_3CH$_2$O), 1.55 – 1.78 (m, 4 H, (CH_2)$_2$), 2.7 – 3.1 (m, 4 H, (CH_2)$_2$N)), 3.7 (q, 1 H, *bridgehead*), 4.2 [q, 2 H, CH$_3$CH_2O), 5.9 (s, 2 H, NH_2). – MS (EI, 70 eV): *m/z* (%) = 256 (11) [$M^+ + 4$], 223 (1) [M^+ -Et], 149 (100, base peak). – $C_{12}H_{16}N_2O_2S$ (252.34): calcd. C 57.11, H 6.39, N 11.10; found C 57.32, H 6.41, N 11.21.

*Phenyl-(1-aza -3-phenyl-5-thia-tricyclo[5.2.2.0^{2,6}]undeca-2(6),3-dien-4-yl)amine (**23**)*

A mixture of **5** (0.5 g, 2 mmol) and phenyl isothiocyanate (0.24 ml, 2 mmol) in NaOMe-MeOH (0.046 g Na, 2 mmol, in 10 ml MeOH) was refluxed for 5 h. The reaction mixture was cooled and poured into ice water to give a grey precipitate which was filtered off, washed with water and dried to give 0.52 g of compound **29**. It was purified by preparative chromatography on Al_2O_3 using pet. ether 40 – 60 °C/ethyl acetate (2:3) as eluent. – M. p. 70 °C. – Yield 78%. – $R_f = 0.6$ (pet. ether 40 – 60 °C/ethyl acetate (2:3)). – IR (KBr): $\tilde{\nu} = 1087$ (C-S), 3216 cm^{-1} (NH). – MS (EI, 70 eV): *m/z* (%) = 333 (0.1) [$M^+ + 1$], 332 (1) [M^+], 255 (2) [M^+-Ph], 239 (1) [M^+-PhNH], 93 (100, base peak). – $C_{21}H_{20}N_2S$ (332.4): calcd. C 75.88, H 6.07, N 8.43; found C 75.94, H 6.23, N 8.51.

*1-Aza 4-[6-Hydroxy-9-phenyl-1,2,3,4,9,9a-hexahydro-10-oxa-1,4-ethano-anthracene-4a-yl]-1,3-dihydroxybenzene (**24**)*

A solution of **5** (0.5 g, 2 mmol) and resorcinol (1.33 g, 12 mmol) in 10% HCl (0.8 ml) was refluxed while stirring in CH_2Cl_2/Et_2O. The solvent was evaporated under vacuum to give 0.6 g of **24** which was crystallized from H_2O. – M. p. 255 °C (water). – Yield 72% (grey crystals). – IR (KBr): $\tilde{\nu} =$ 3430, 3490 cm^{-1} (OH). – ^1H NMR (200 MHz [D_6]-DMSO): $\delta = 2.07$ (m, 4 H, (CH_2)$_2$C), 2.45 ([q, 1 H, *bridgehead*), 3.23 (m, 4 H, (CH_2)$_2$N), 3.85 (d, $J = 9.6$ Hz 1 H, N-C*H*-C-), 4.33 (d, $J = 8.6$ Hz, 1 H, Ph-C*H*-Ph), 6.14 – 7.47 (m, 11 H, *arom.*, 9.75 (m, 3 H, 3(O*H*)). – MS (EI, 70 eV): *m/z* (%) = 416 (2) [$M^+ + 1$], 414 (2) [$M^+ - 1$], 210 (2) [M^+-3OH-2Ph], 132 (100, base peak). – $C_{25}H_{25}NO_4$ (415.22): calcd. C 75.02, H 6.24, N 3.36; found C 75.13, H 6.32, N 3.41.

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