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Synthesis of Hexahydro-*1H*-pyrido[3,2-*c*]azepines as Hypotensive Agents of Expected Calcium-Channel Blocking Activity

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Summary. *Michael* addition reaction of 3-(4-fluorophenylamino)-2-cyclohexenone and its 5,5-dimethyl derivative to the acrylonitrile derivatives afforded the novel hexahydroquinolines. The target hexahydro-*1H*-pyrido[3,2-*c*]azepine derivatives were obtained *via* ring enlargement of the corresponding hexahydroquinolines under *Schmedt* conditions.

Some novel pyrido[3,2-*c*]azepines showed hypotensive activity *in vivo* on normotensive anaesthetized male adult albino rats and their effects on the ventricular contraction and auricular rate of isolated rabbit hearts using *Langendorff*'s method and nefidipine as a reference drug were studied. Compounds **29** and **36** which bear some structural similarities to nefidipine exhibited the highest hypotensive activity and negative inotropic as well as chronotropic activities.

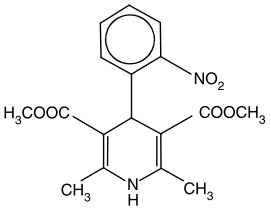
Keywords. Hexahydroquinolines; Pyrido[3,2-*c*]azepines; Hypotensive activity; Nefidipine.

Introduction

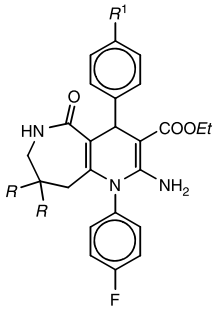
Pyridoazepine based systems have a variety of biological activities through binding to different molecular targets *in vivo* such as H_1 antagonists [1], angiotensin-converting enzyme inhibitors [2], M_1 antagonistic activity [3], A_3 adenosine receptor antagonists [4], natriuretic and hypotensive activities [5].

Among the classes of calcium-channel blockers, dihydropyridine derivatives *e.g.* nifedipine have a special significance in the therapy of hypertension, angina pectoris, and other cardiovascular diseases [6, 7]. This may be due to decrease the myocardial oxygen demand by reducing heart rate, blood pressure, or myocardial contractility [8] and to increase the myocardial oxygen supply by enhancing coronary blood flow as well as preventing coronary vasospasm [7].

This motivated us to synthesize a novel series of pyrido[3,2-*c*]azepine based derivatives which are somewhat structurally related to the dihydropyridine calcium antagonist nifedipine with the aim to have hypotensive effects with expected calcium-channel blocking activity.



Nifedipine



29: R = H, R^1 = Cl

36: R = CH_3, R^1 = NO_2

Results and Discussion

Chemistry

In this work, the novel pyrido[3,2-*c*]azepine derivatives **24**–**36** were designed and prepared as illustrated in Scheme 1.

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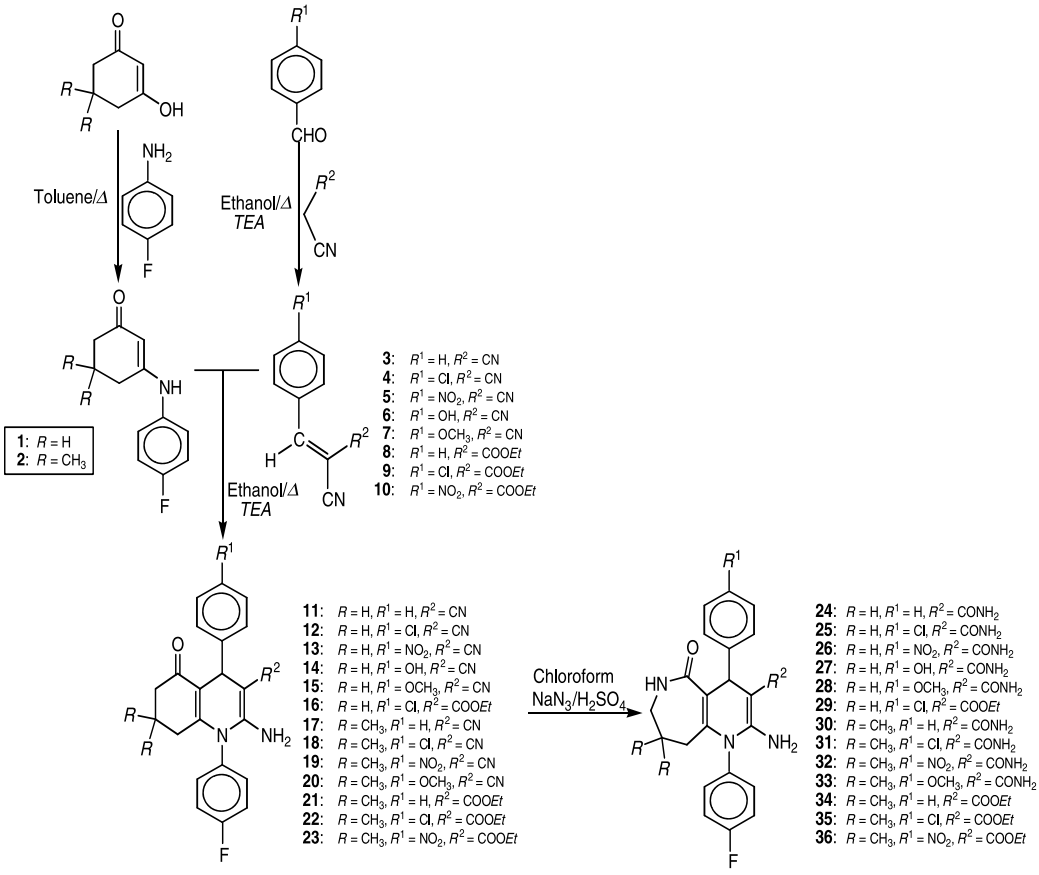

Scheme 1

The intermediates 3-(4-fluorophenylamino)-2-cyclohexenone or its 5,5-dimethyl derivative **1** and **2** were prepared by condensation of equimolar amounts of 1,3-cyclohexandione or its 5,5-dimethyl derivative with 4-fluoroaniline *via* heating the reactants under reflux in toluene [9–12].

2-Cyanoacrylonitriles or their ethyl ester analogs **3–10** were synthesized by the reaction of aromatic aldehydes with malonodinitrile or ethyl cyanoacetate in ethanol containing catalytic amount of triethylamine (*TEA*) [13–17].

We here report the synthesis of hexahydroquinolines **11–23** through *Michael* addition reaction [18, 19] of enaminones **1** and **2** to different 2-cyanoacrylonitriles and their ethyl ester analogs **3–10** by heating the reactants at reflux in ethanol in the presence of *TEA*.

The structure of the novel hexahydroquinolines **12**, **15–17** was assigned using elemental analyses as well as IR, ^{1}H NMR, and mass spectroscopic methods. IR data for compound **12** showed two absorption bands at 3466 and 3320 cm^{-1} due to asym. and sym. stretching vibrations of NH_2 group. Likewise, the appearance of a band at 2182 cm^{-1} is due to the nitrile function as well as a strong absorption band at 1640 cm^{-1} signifies the presence of a carbonyl function. In addition, the ^{1}H NMR showed a very characteristic singlet peak in the range from $\delta = 4.41$ to 4.96 ppm integrating one proton of the 4*H*-pyridine nucleus.

In the present investigation, the fact that the *Schmidt* reaction [20, 21] with a ketone gives an azidohydrin intermediate, which rearranges to form an amide was utilized in the conversion of hexahydroquinolines **11–23** to the corresponding novel hexahydro-*1H*-pyrido[3,2-*c*]azepines **24–36**.

These compounds were characterized using melting points, mixed melting points, and thin layer chromatography techniques in different solvent systems. Moreover, the structures of pyrido[3,2-*c*]azepines were established using elemental analyses and various spectroscopic methods.

IR data showed two absorption bands in the range 3460 and 3320 cm^{-1} for NH_2 group. The strong

absorption band at 1657 cm^{-1} signifies the presence of an ester function. The ^1H NMR showed a very characteristic singlet peak in the range from $\delta = 4.51$ to 5.00 ppm integrating one proton of the 4*H*-pyridine nucleus.

Pharmacology

Calcium antagonists are a heterogeneous group of agents, all leading to inhibition of calcium influx into myocardial and vascular smooth muscle cells. In the isolated heart, calcium antagonists cause significant depression of the SA node function and a profound negative inotropic effect [6, 8].

These adverse effects are not usually seen with therapeutic doses of calcium antagonists *in vivo* due to the decrease of the vascular resistance after administration of calcium antagonists which causes a fall in mean arterial pressure and elicits adrenergic reflexes which counteract the SA node depression and the negative inotropic effect [7].

Thus, we prepared a novel series of pyrido[3,2-*c*] azepines which bears some structural similarities to nefidipine in order to study their effects on arterial blood pressure of anaesthetized male adult albino rats [22–24] as well as to examine their inotropic and chronotropic activities on isolated rabbit hearts using *Langendorff*'s method [25, 26].

These similarities are: 1) the nefidipine and pyrido[3,2-*c*]azepines structures contain partially saturated pyridine ring, 2) substituted phenyl group at 4-position, 3) ethyl ester group at 3-position for some derivatives, 4) the methyl group at 2-position of nefidipine is replaced by its isosteric amino group in pyrido[3,2-*c*]azepines, 5) the ester moiety at 5-position of nefidipine is replaced by its isosteric cyclized amide moiety in pyrido[3,2-*c*]azepines, 6) the secondary amine at 1-position of nefidipine, which is easily oxidized *in vivo* to inactive pyridine metabolite [27], is protected by *p*-fluorophenyl group due to formation of the tertiary amine in pyrido[3,2-*c*]azepines.

A) Hypotensive Activity

Screening the effect of the novel pyrido[3,2-*c*]azepines **24**–**36** on the arterial blood pressure of anaesthetized male adult albino rats revealed that **24**, **27**, **28**, **31**, and **33** did not have any effect on the arterial blood pressure and were excluded. Meanwhile, **25**, **26**, **29**, **30**, **32**, and **34**–**36** that showed a hypotensive activity (Table 1) were used to study their inotropic and chronotropic activities.

The compounds tested at doses lower than 3 mg/kg and also solvent-treated group which had the same concentration of tween 80 as in the test solution do not record any response. Nefidipine (3 mg/kg)

Table 1. Effect of nefidipine and compounds **25**, **26**, **29**, **30**, **32**, and **34**–**36** on the systolic (SABP), diastolic (DABP) arterial blood pressure of anaesthetized male adult albino rats ($n = 6$). Values represent mean ± S.D.

Comp no.	Dose/mg kg^{-1}	Systolic BP/Torr	Mean change	Diastolic BP/Torr	Mean change
Control	0.0	125 ± 3.2	–	95 ± 2.1	–
Nefidipine	3.0	70 ± 2.5***	↓44%	60 ± 2.7***	↓37%
Control	0.0	120 ± 1.5	–	90 ± 3.6	–
25	3.0	105 ± 3.2*	↓12%	85 ± 2.4*	↓6%
Control	0.0	160 ± 5.4	–	130 ± 5.2	–
26	3.0	155 ± 3.2	↓3%	125 ± 4.1	↓4%
Control	0.0	140 ± 3.8	–	80 ± 2.9	–
29	3.0	115 ± 3.4**	↓18%	55 ± 3.0***	↓31%
Control	0.0	135 ± 2.6	–	105 ± 2.3	–
30	3.0	125 ± 3.0*	↓7%	100 ± 2.1	↓5%
Control	0.0	180 ± 5.3	–	160 ± 3.5	–
32	3.0	170 ± 3.1	↓6%	150 ± 3.6*	↓6%
Control	0.0	160 ± 5.5	–	100 ± 2.8	–
34	3.0	140 ± 4.3*	↓13%	90 ± 3.1*	↓10%
Control	0.0	115 ± 3.8	–	90 ± 2.1	–
35	3.0	110 ± 2.5	↓4%	90 ± 1.9	0%
Control	0.0	130 ± 2.7	–	100 ± 3.6	–
36	3.0	100 ± 3.0***	↓23%	80 ± 2.2**	↓20%

* $P < 0.05$, ** $P < 0.001$, *** $P < 0.0001$ compared with control; *n* Number of experiment on each parameter

produced significant ($P<0.0001$) reduction in both systolic and diastolic arterial blood pressure (SABP and DABP) where the maximum response was noticed 15 min after intraperitoneal injection (i.p.).

Regarding the parent compounds **24**, **30**, and **34** which have unsubstituted phenyl group at 4-position, it was noted that the 8,8-dimethyl derivative **30** containing carboxamide functionality at 3-position showed reduction in BP while its non-methylated analog **24** did not show any effect. Meanwhile, replacement of carboxamide group of compound **30** by the ester functionality at the same position increased the activity as shown in **34** (Table 1). The rank order of activity for the parent compounds is **34** > **30** > **24**. This is also true for the compounds containing *p*-nitrophenyl group at 4-position (Table 1) whereas the rank order of activity is **36** > **32** > **26**. In contrast, the order of activity for the compounds containing *p*-chlorophenyl group at 4-position is **29** > **25** > **35** (Table 1).

B) Inotropic and Chronotropic Activities

Besides the hypotensive activity for the compounds **25**, **26**, **29**, **30**, **32**, and **34**–**36**, their inotropic and chronotropic activities were studied on isolated rabbit hearts using *Langendorff*'s method [25, 26] and nefidipine as a reference drug. The % reductions from the normal in both ventricular contraction and auricular rate were recorded after 5 min as illustrated in Table 2.

It was observed from Table 2 that the parent compound **34** (with unsubstituted phenyl at 4-position) having 8,8-dimethyl group and ester functionality at 3-position showed a higher % reductions in both ventricular contraction and auricular rate than compound **30** which possesses carboxamide functionality at 3-position while the non-methylated analog (compound **24**) has no effect on the heart.

For compounds **26**, **32**, and **36** which containing *p*-nitrophenyl group at 4-position, it was observed that compounds **32** (8,8-dimethyl derivative) and **26** (non-methylated analog) with carboxamide functionality at 3-position, have no inotropic effect while compound **36** containing the 8,8-dimethyl group and ester functionality at 3-position showed the highest negative inotropic (40%) and chronotropic (33%) effects in comparison with nefidipine (Table 2).

Regarding the compounds containing *p*-chlorophenyl group at 4-position (**29** and **35**), it was noted that the non-methylated derivative **29** with ester functionality at 3-position exhibited a higher % reductions in both ventricular contraction (33%) and auricular rate (25%) than its methylated analog **35** (Table 2).

Table 2. Effect of compounds **25**, **26**, **29**, **30**, **32**, and **34**–**36** on the inotropic and chronotropic activities of isolated rabbit hearts ($n=4$)

Comp. no.	% Reduction in inotropic activity	% Reduction in chronotropic activity
Nefidipine	29 ± 1.5	21 ± 0.46
25	11 ± 0.26	22 ± 0.3
26	00.0	12.5 ± 0.28
29	33 ± 0.82	25 ± 0.62
30	16 ± 0.46	9.0 ± 0.23
32	00.0	12.5 ± 0.18
34	21.5 ± 0.52	23 ± 0.55
35	9 ± 0.19	10 ± 0.23
36	40 ± 2.3	33 ± 0.5

Conclusions

Hexahydroquinoline intermediates were synthesized and then utilized for preparation of the target hexahydro-1*H*-pyrido[3,2-*c*] azepines under *Schmidt* conditions.

Compounds **29** and **36** showed the highest reduction in BP and ventricular contraction as well as auricular rate. These compounds are characterized by *p*-substituted phenyl with electron withdrawing group (Cl, NO_2) at 4-position [6] and ester functionality at 3-position of the partially saturated pyridine ring which seems similar to the calcium antagonist nefidipine. Moreover, it is clear from this study that the 8,8-dimethyl group is not essential for activity as shown in compounds **29** and **36**. Such negative inotropic and chronotropic effects strengthen the hypothesis that these compounds may exert their effects through voltage dependent calcium channel blocking mechanism (L-type) due to the structural similarity of these compounds with nifedipine [27].

Experimental

General

Melting points were determined with a *Gallenkamp* digital melting point apparatus in open capillaries. IR spectra (KBr) were recorded using *Bruker* spectrophotometer. ^{1}H NMR spectra were determined on *Varian Gemini* 200 MHz using *DMSO*-d_6 as a solvent and *TMS* as an internal standard (chemical shifts in δ, ppm). Mass spectra were measured on

a GCMS-QP1000EX-*SHIMADZU* with ionization energy 70 eV. Elemental analyses were performed at the Microanalytical Center, Faculty of Science, Cairo University, Giza, Egypt. Their results corresponded to the calculated values within experimental error. TLC was performed on silica gel G (Fluka) and spots were visualized by iodine vapors or irradiation with UV light (254 nm). The starting materials were purchased from Sigma-Aldrich. The intermediates 3-(4-fluorophenylamino)-2-cyclohexenone or its 5,5-dimethyl derivative **1**–**2** [9, 10] and 3-aryl-2-substituted acrylonitriles **3**–**10** [13–17] were prepared according to the reported procedures.

*General Procedure for the Preparation of **11**–**23***
A mixture of equimolar amounts of enaminones **1** or **2** and the appropriate 3-aryl-2-substituted acrylonitrile **3**–**10** (1 mmol) in 15 cm^3 *Et*OH containing four drops *TEA* was heated under reflux for 12 h. The reaction mixture was cooled, and the separated product was filtered off, washed with water, and recrystallized from aqueous dioxane.

2-Amino-1-(4-fluorophenyl)-4-(4-chlorophenyl)-3-cyano-5-oxo-1,4,5,6,7,8-hexahydroquinoline (**12**, $C_{22}H_{17}ClFN_3O$)
Yield 48%; mp 306–308°C; IR: $\bar{\nu} = 3466$, 3320 (NH_2), 3049 (CH, aromatic), 2973 (CH, aliphatic), 2182 (CN), 1662 (C=O) cm^{-1}.

2-Amino-1-(4-fluorophenyl)-4-(4-methoxyphenyl)-3-cyano-5-oxo-1,4,5,6,7,8-hexahydroquinoline (**15**, $C_{23}H_{20}FN_3O_2$)
Yield 43%; mp 284–286°C; ^{1}H NMR: $\delta = 1.62$–1.69 (m, 7-CH_2), 1.83–1.92 (m, 6-CH_2), 2.19–2.20 (m, 8-CH_2), 3.74 (s, OCH_3), 4.45 (s, 4-CH), 5.45 (s, NH_2, exch), 6.86–7.44 (m, ArH) ppm.

2-Amino-1-(4-fluorophenyl)-4-(4-chlorophenyl)-3-ethoxycarbonyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline (**16**, $C_{24}H_{22}ClFN_2O_3$)
Yield 35%; mp 202–204°C; ^{1}H NMR: $\delta = 1.09$–1.16 (t, 3H, $COOCH_2CH_3$), 1.57–1.62 (m, 7-CH_2), 1.80–1.87 (m, 6-CH_2), 2.18–2.20 (m, 8-CH_2), 3.93–3.99 (q, 2H, $COOCH_2$), 4.96 (s, 4-CH), 6.88 (br s, NH_2, exch), 7.20–7.52 (m, 8ArH) ppm.

2-Amino-1-(4-fluorophenyl)-4-phenyl-3-cyano-7,7-dimethyl-5-oxo 1,4,5,6,7,8-hexahydroquinoline (**17**, $C_{24}H_{22}FN_3O$)
Yield 50%; mp 268–270°C; MS: m/z (%) = 387 (M^+, 22.1), 310 (100).

*General Procedure for the Preparation of **24**–**36***
Sodium azide (4 mmol) was added over a period of 40 min to a stirred mixture of the hexahydroquinoline derivatives **11**–**23** (1 mmol) in chloroform and 1 cm^3 concentrated sulfuric acid. The reaction mixture was then stirred 12 h at room temperature. After the addition of ice water and neutralization of the mixture with solid sodium bicarbonate, the layers were separated and the water layer was extracted three times with 50 cm^3 chloroform. The chloroformic extract was dried over anhydrous sodium sulfate and then evaporated using rotary evaporator. The separated product was recrystallized using methanol.

2-Amino-1-(4-fluorophenyl)-4-phenyl-3-aminocarbonyl-5-oxo-4,5,6,7,8,9 hexahydro-1H-pyrido[3,2-c]azepine (**24**, $C_{22}H_{21}FN_4O_2$)
Yield 20%; mp 227–229°C; ^{1}H NMR: $\delta = 1.65$–1.70 (m, 8-CH_2), 2.05–2.12 (m, 7-CH_2), 2.80–2.85 (m, 9-CH_2), 4.51 (s, 4-CH), 5.24 (s, NH_2), 7.29–7.47 (m, 12H, ArH + NH, +$CONH_2$) ppm.

2-Amino-1-(4-fluorophenyl)-4-(4-chlorophenyl)-3-aminocarbonyl-5-oxo-4,5,6,7,8,9-hexahydro-1H-pyrido[3,2-c]azepine (**25**, $C_{22}H_{20}ClFN_4O_2$)
Yield 26%; mp 272–274°C; IR: $\bar{\nu} = 3424$, 3326, 3241, 3169 (NH), 3067 (CH, aromatic), 2961 (CH, aliphatic), 1664, 1625 (C=O) cm^{-1}; MS: m/z (%) = 426 (M^+, 1.7), 410 (1.4), 398 (1.0), 382 (100), 315 (7.5).

2-Amino-1-(4-fluorophenyl)-4-(4-nitrophenyl)-3-aminocarbonyl-5-oxo-4,5,6,7,8,9-hexahydro-1H-pyrido[3,2-c]azepine (**26**, $C_{22}H_{20}FN_5O_4$)
Yield 30%; mp 274–276°C; IR: $\bar{\nu} = 3462$, 3413, 3319, 3245, 3202 (NH), 3069 (CH, aromatic), 2925 (CH, aliphatic), 1663, 1628 (C=O) cm^{-1}; ^{1}H NMR: $\delta = 1.7$–1.8 (m, 8-CH_2), 2.08–2.12 (m, 7-CH_2), 2.80–2.90 (m, 9-CH_2), 4.95 (s, 4-CH), 6.22 (s, NH_2, exch), 7.1 (s, $CONH_2$, exch), 7.38–8.17 (m, 9H, ArH + NH, exch) ppm; MS: m/z (%) = 437 (M^+, 3.7), 420 (3.4), 393 (100), 366 (4.1), 315 (5.2).

2-Amino-1-(4-fluorophenyl)-4-(4-hydroxyphenyl)-3-aminocarbonyl-5-oxo-4,5,6,7,8,9-hexahydro-1H-pyrido[3,2-c]azepine (**27**, $C_{22}H_{21}FN_4O_3$)
Yield 22%; mp 255–256°C; IR: $\bar{\nu} = 3461$(OH), 3316, 3217, 3185 (NH), 3048 (CH, aromatic), 2923 (CH, aliphatic), 1662 (C=O) cm^{-1}.

2-Amino-1-(4-fluorophenyl)-4-(4-methoxyphenyl)-3-aminocarbonyl-5-oxo-4,5,6,7,8,9-hexahydro-1H-pyrido[3,2-c]azepine (**28**, $C_{23}H_{23}FN_4O_3$)
Yield 18%; mp 254–255°C; IR: $\bar{\nu} = 3414$, 3317, 3213 (NH), 3057 (CH, aromatic), 2959 (CH, aliphatic), 1661 (C=O) cm^{-1}.

2-Amino-1-(4-fluorophenyl)-4-(4-chlorophenyl)-3-ethoxycarbonyl-5-oxo-4,5,6,7,8,9-hexahydro-1H-pyrido[3,2-c]azepine (**29**, $C_{24}H_{23}ClFN_3O_3$)
Yield 15%; mp 275–277°C; IR: $\bar{\nu} = 3473$, 3299 (NH), 3049 (CH, aromatic), 2976 (CH, aliphatic), 1658(C=O) cm^{-1}; ^{1}H NMR: $\delta = 1.01$–1.06 (t, 3H, $COOCH_2CH_3$), 1.7–1.8 (m, 8-CH_2), 2.08–2.10 (m, 7-CH_2), 2.7–2.8 (m, 9-CH_2), 3.9–3.99 (q, 2H, $COOCH_2$), 4.83 (s, 4-CH), 6.8 (br s, NH_2, exch), 7.27–7.48

(m, 9H, ArH + NH, exch) ppm; MS: m/z (%) = 455 (M^+, 8.6), 410 (12.0), 382 (74.7), 344 (100).

2-Amino-1-(4-fluorophenyl)-4-phenyl-8,8-dimethyl-3-aminocarbonyl-5-oxo-4,5,6,7,8,9-hexahydro-1H-pyrido[3,2-c]azepine (**30**, $C_{24}H_{25}FN_4O_2$)
Yield 30%; mp 232–233°C; ^{1}H NMR: $\delta = 0.47$ (s, CH_3), 0.71 (s, CH_3), 2.0–2.2 (m, 4H, 7-CH_2 + 9-CH_2), 4.54 (s, 4-CH), 5.17 (s, NH_2, exch), 7.29–7.41 (m, 10H, ArH + NH, exch), 7.8 (s, $CONH_2$, exch) ppm.

2-Amino-1-(4-fluorophenyl)-4-(4-chlorophenyl)-8,8-dimethyl-3-aminocarbonyl-5-oxo-4,5,6,7,8,9-hexahydro-1H-pyrido[3,2-c]azepine (**31**, $C_{24}H_{24}ClFN_4O_2$)
Yield 35%; mp 246–248°C; MS: m/z (%) = 454 (M^+, 1.6), 437 (2.9), 426 (1.3), 410 (100), 383 (12.8), 343 (5.6).

2-Amino-1-(4-fluorophenyl)-4-(4-nitrophenyl)-8,8-dimethyl-3-aminocarbonyl-5-oxo-4,5,6,7,8,9-hexahydro-1H-pyrido[3,2-c]azepine (**32**, $C_{24}H_{24}FN_5O_4$)
Yield 37%; mp 251–253°C; IR: $\bar{\nu} = 3461$, 3325, 3214 (NH), 3075 (CH, aromatic), 2953 (CH, aliphatic), 1657, 1628 (C=O) cm^{-1}; MS: m/z (%) = 465 (M^+, 1.0), 448 (1.9), 437 (0.3), 422 (100), 394 (11.8), 343 (2.2).

2-Amino-1-(4-fluorophenyl)-4-(4-methoxyphenyl)-8,8-dimethyl-3-aminocarbonyl-5-oxo-4,5,6,7,8,9-hexahydro-1H-pyrido[3,2-c]azepine (**33**, $C_{25}H_{27}FN_4O_3$)
Yield 17%; mp 279–280°C; IR: $\bar{\nu} = 3450$, 3421, 3334, 3206 (NH), 3076 (CH, aromatic), 2953 (CH, aliphatic), 1656, 1628 (C=O) cm^{-1}.

2-Amino-1-(4-fluorophenyl)-4-phenyl-8,8-dimethyl-3-ethoxycarbonyl-5-oxo-4,5,6,7,8,9-hexahydro-1H-pyrido[3,2-c]azepine (**34**, $C_{26}H_{28}FN_3O_3$)
Yield 14%; mp 223–225°C; ^{1}H NMR: $\delta = 0.42$ (s, CH_3), 0.68 (s, CH_3), 1.05–1.10 (t, 3H, $COOCH_2CH_3$), 2.08–2.09 (m, 4H, 7-CH_2 + 9-CH_2), 3.91–3.98 (q, 2H, $COOCH_2$), 4.9 (s, 4-CH), 6.7 (br s, NH_2, exch), 7.25–7.42 (m, 9ArH),7.80 (br s, NH, exch) ppm.

2-Amino-1-(4-fluorophenyl)-4-(4-chlorophenyl)-8,8-dimethyl-3-ethoxycarbonyl-5-oxo-4,5,6,7,8,9-hexahydro-1H-pyrido[3,2-c]azepine (**35**, $C_{26}H_{27}ClFN_3O_3$)
Yield 19%; mp 289–290°C; IR: $\bar{\nu} = 3467$, 3287 (NH), 3055 (CH, aromatic), 2959 (CH, aliphatic), 1657 (C=O) cm^{-1}; MS: m/z (%) = 483 (M^+, 7.2), 438 (9.7), 410 (78.9), 372 (100).

2-Amino-1-(4-fluorophenyl)-4-(4-nitrophenyl)-8,8-dimethyl-3-ethoxycarbonyl-5-oxo-4,5,6,7,8,9-hexahydro-1H-pyrido[3,2-c]azepine (**36**, $C_{26}H_{27}FN_4O_5$)
Yield 20%; mp 285–287°C; ^{1}H NMR: $\delta = 0.47$ (s, CH_3), 0.70 (s, CH_3), 1.01–1.06 (t, 3H, $COOCH_2CH_3$), 2.0–2.2 (m, 4H, 7-CH_2 + 9-CH_2), 3.90–3.99 (q, $COOCH_2$), 5.0 (s, 4-CH), 6.8 (br s, NH_2, exch), 7.41–8.18 (m, 9H, ArH + NH, exch) ppm.

Pharmacology

A) Hypotensive Activity

Materials and methods: Sixty male adult albino rats weighing 180–220 g were classified into ten groups; each consisted of 6 rats. All the test compounds were dissolved in tween 80 and diluted with distilled water to the final volume (1:3). These groups were used to study the effect of solvent, nefidipine (*Sigma* Chemicals Co., USA), and the test compounds **25**, **26**, **29**, **30**, **32**, and **34**–**36** on the arterial blood pressure, which were recorded 15 min after i.p. injection of 3 mg/kg of each compound.

Method of recording of the arterial blood pressure: Animals were anaesthetized with ethyl carbamate in a dose of 1.75–2.0 g/kg i.p. as freshly prepared aqueous solution [22]. The blood pressure was determined employing the method of *Burden* [23] through introduction of polyethylene arterial cannula with 3-way valve (filled with heparinized saline solution 16 I.U./cm^3 to inhibit blood clotting) in the common carotid artery. The cannula was connected to PT 400 blood pressure transducer, which was connected to FC137 strain gauge coupler which was fixed to one of the 4-channel oscillograph MD_4 (Bioscience, U.K.). The blood pressure was recorded on chart paper.

The values of the systolic and diastolic arterial blood pressure were presented in Table 1 as mean ± S.D. and subjected to one-way ANOVA test for statistical analysis [24].

B) Determination of Inotropic and Chronotropic Activities (*Langendorff*'s Method)

The apparatus was prepared before the animal was sacrificed and designed to supply warm (37°C) and oxygenated *Ringer-Locke* solution to the suspended heart.

Ringer-Locke solution of the following composition (g/dm^3) was used: NaCl (9.0 g), KCl (0.42 g), $CaCl_2$ (0.24 g), $NaHCO_3$ (0.50 g), glucose (2.0 g), distilled water up to 1000 cm^3.

The rabbit was sacrificed and the heart was cleaned and then fixed through the aorta to the cannula of *Langendorff*'s apparatus [25, 26] which was connected through a glass spiral of 50 cm^3 capacity to two reservoirs *via* a Y-shape glass connection with clamps at both limbs to allow passage of the solution as required. A hook was attached to the ventricular wall of the heart and was attached by a thread to the lever of one T_2 isotonic transducer, after passing over pulley wheels. Also, a small spring clip was attached to the right auricle and was attached to the lever of the other T_2 isotonic transducer.

The normal (control) ventricular and auricular performance of the heart perfused with oxygenated *Ringer-Locke* solution were recorded on the paper chart using alternative speeds 0.25 and 25 mm/sec, this allowed detection of any change in the amplitude of the beats (contractility or inotropic effect) and the rate of beating (chronotropic effect), respectively.

The reference drug nefidepine or the test compound **25**, **26**, **29**, **30**, **32**, and **34**–**36** is then injected as a single shot into the rubber of the aortic cannula with the resultant concentration of

$10\,\mu g/cm^3$ in the perfusion liquid. The inotropic and chronotropic effects of the nefidipine or the new compounds were recorded after 5 min and were expressed as % change from the control values (Table 2).

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