A PREPARATIVE ROUTE TO FUSED INDENO[1,2-*e*][1,2,4]-TRIAZOLO[4,3-*a*]PYRAZIN-4-ONES

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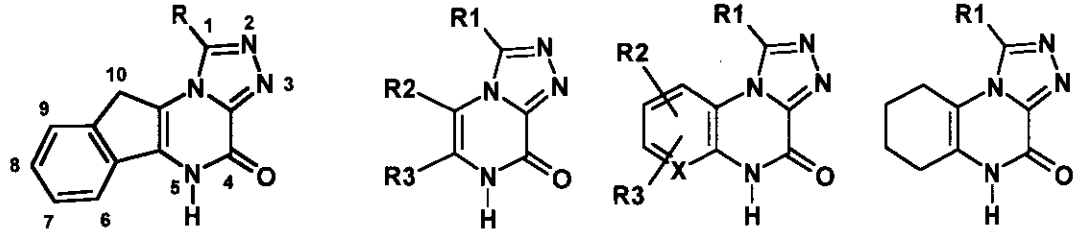
Abstract- Syntheses of new fused indeno[1,2-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-4-one derivatives **(1a-g)** starting from 1-indanone are described .

Excessive stimulation of L-glutamate receptors has been reported as being implicated in neuronal death as a consequence of cerebral ischemia , epilepsy and neurodegenerative diseases. [1] Competitive or non-competitive antagonists of these biological targets (such as AMPA) acting at the *N*-methyl-D-aspartate (NMDA) subtype have been proposed as potential neuroprotective agents in human. [2] In connection with our own research projects directed towards the synthesis of such potent AMPA antagonists, [3] an easy and efficient method leading to new fused indeno[1,2-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-4-one derivatives (**1a-g**) has been developed (Figure 1).

To our knowledge, only 1,2,4-triazolo[4,3-*a*]pyrazin-4-one (**2a**), [4] 1,2,4-triazolo[4,3-*a*]quinoxalin-4-one (**2b**), [5] 1,2,4-triazolo[4,3-*a*]pyrido[3,2-*e*]pyrazin-4-one (**2c**), [6] and 6,7,8,9-tetrahydro-1,2,4-triazolo[4,3-*a*]quinoxalin-4-one (**2d**) [7] derivatives were already described (Figure 1).

Figure 1



1a	b	c	d	e	f	g
R-: H	Me-	Et-	*n*-Bu-	*iso*-Pro	cyclo-Pro	H_2N-

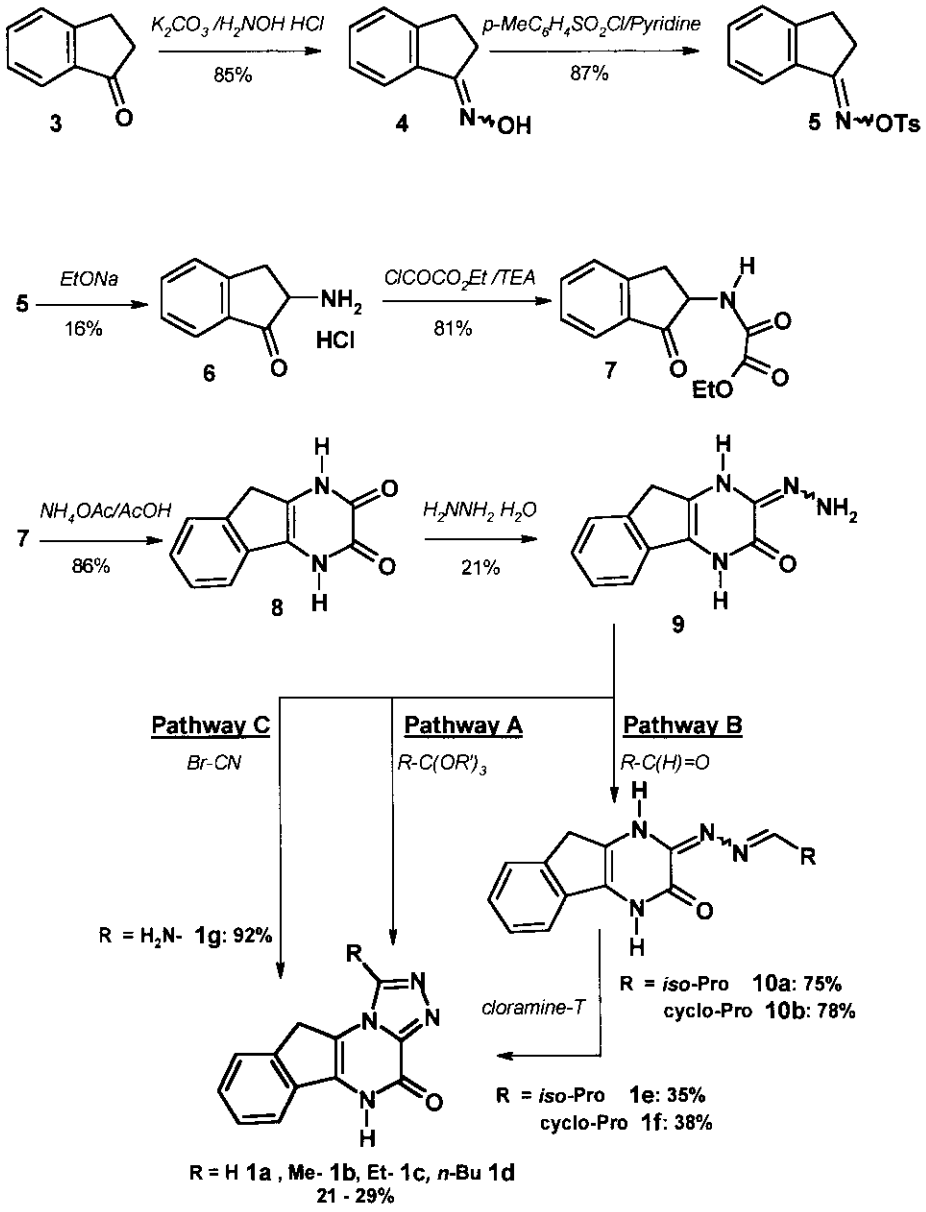
We therein report the efficient synthesis of new triazolopyrazin-8-one derivatives (**1a-1g**) [8] bearing various substituents in position 1 , within a seven to eight steps synthesis as summarized in Scheme 1.

Our strategy started from the commercially available 1-indanone (**3**) , while cyclization of the key intermediate **9** was finally performed using either : i) various orthoesters addition (Pathway A) ; ii) aldehydes condensation followed by action of chloramine-T (Pathway B) or iii) cyanogen bromide enclosing (Pathway C) .

As previously described [9,10] **3** gave **6** in 3 steps in a moderate overall yield of 12% . Then , *N*-acylation of **6** followed by ring closure step -using ammonium acetate in presence of acetic acid (at reflux)- gave the original 1,4-dihydro-5*H*-indeno[1,2-*b*]pyrazine-2,3-dione (**8**) in 70% overall yield. Then the hydrazono-indenopyrazinone derivative (**9**) was finally isolated in 21% yield. With **9** in hand, we performed the

synthesis of the triazolopyrazin-4-one derivatives.

Scheme 1



According to Pathway A, a direct cyclization with orthoesters [11] afforded the expected compounds (**1a-d**) in ~30% yield. Introduction of other alkyl groups in position 1 of the indeno[1,2-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-4-one nucleus was readily achieved by condensation of adequate aldehydes leading to derivatives (**10a,b**) in ~75% yield , followed by a ring closure using chloramite-T giving **1e-f** in ~35% yield (Pathway B). [12] Introduction of an amino group was carried out directly by action of cyanogen bromide at room temperature giving **1g** in a 92% yield (Pathway C). [13] In conclusion, we have developed , from 1-indanone , several synthetic routes towards a wide variety of new indeno[1,2-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-4-one derivatives (**1a-g**). [14]

EXPERIMENTAL

Commercially available reagents were used as received from suppliers, while solvents were dried in the classical way. The progresses of the reactions were monitored using TLC on silica gel plates (Merck Kieselgel $60F_{254}$). Melting points were determined on a Reicher-Kofler instrument and are uncorrected. Final compounds (**1a-1f**) were recrystallized except **1g** due to its very poor solubility . ^{1}H NMR spectra were recorded using AC 200, AC 300 and Avance 600 Bruker spectrometers. Chemical shifts are given in ppm (δ DMSO = 2.5) while J coupling constants are expressed in Hz. IR spectra were recorded on a FT-IR 60SX-R Nicolet spectrophotometer , samples being dispersed as a KBr pellet or in solution (CH_2Cl_2). MS spectra were obtained on a Finnigan 4000 (EI, 70eV) or on a Nermag R10-10B (DCI, NH_3) mass spectrometers. Elemental analyses (C,H,N,) were only performed on compounds of interest (**1a-1g**) using a Carlo Erba 1108 microanalyzer.

1-Indanone oxime (4)

A stirred solution of 1-indanone (**3**) (100.2 g, 0.76 mol), potassium carbonate (183.3 g, 1.3 mol) and hydroxylamine hydrochloride (183.1 g, 2.6 mol) in methanol (1.7 L) and water (170 mL) was heated to reflux overnight. The reaction mixture was cooled to rt, and the precitate thus obtained was filtered, washed with water and methanol to afford 95.6 g (85%) of **4** as white solid, mp 154°C, lit., [10] 144°C.

1-Indanone-*O*-tosyloxime (5)

To a stirred solution of **4** (95.6 g, 1.3 mol) in dry pyridine (900 mL) at 0°C, kept under nitrogen, was added *p*-toluenesulfonyl chloride (66.3 g, 1.4 mol) in dry pyridine (60 mL). Then the yellow reaction mixture was stirred for 3 h at the same temperature. The resulting orange solution was poured onto cold water (1.5 L), and the precipitate was filtered, washed with cold water to afford 171 g (87%) of **5** as a white solid, mp 151°C, lit., [10] 157°C.

2-Amino-1-indanone hydrochloride (6)

To a suspension of **5** (1 g, 3 mmol) in dry toluene (20 mL) at 0°C, kept under nitrogen atmosphere, was slowly added a solution of sodium ethoxide - prepared from sodium (0.1 g, 4 mmol) and ethanol (50 mL). The reaction mixture was stirred and carefully kept between -10°C and 0°C overnight. The insoluble was filtered on celite , and the solution was washed with water (10 mL). The organic extract was then treated with 1N HCl until acidic pH of the solution , and was concentrated *in vacuo* . The residue was finally triturated with acetone and filtered to give 0.1 g (17%) of **6** as a brown solid, mp > 260°C, lit., [10] 240°C.

Ethyl *N*-(1-indanon-2-yl)oxamate (7)

To a stirred suspension of **6** (36.7 g, 0.2 mol) in dry CH_2Cl_2 (200 mL) at 0°C, kept under nitrogen atmosphere, ethyl oxalyl chloride (27.4 mL, 0.24 mol) was added dropwise followed by triethylamine (63 mL, 0.44 mol). The reaction mixture was then stirred overnight and allowed to slowly reach rt. The insoluble thus obtained was filtered, and treated with CH_2Cl_2 (2 x 50 mL). All the combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. The residue was triturated with a saturated solution of $NaHCO_3$ (2 x 200 mL) to afford 40 g (81%) of **7** as a pale orange solid, mp 136°C (isopropyl ether). NMR (200 MHz , DMSO) δ : 1.3 (3H, t, J=7, methyl), 3.1 (1H, dd, J=17 and 5, H_3), 3.5 (1H, dd, J=17 and 8, H_3), 4.3 (2H, q, J=7, CH_2O), 4.6 (1H, m, H_2), 7.5 to 7.75 (4H, m, phenyl), 9.5 (1H, d, J=8, NH). MS (DCI) : m/z 248 , MH^+. IR (CH_2Cl_2) cm^{-1} : 3400 , NH ; 1762 , 1705, oxamide ; 1728 , carbonyl .

1,4-Dihydroindeno[1,2-*b*]pyrazine-2,3-dione (8)

To a stirred solution of ammonium acetate (7.5 g, 0.1 mol) in acetic acid (30 mL), under nitrogen and at reflux , **7** (0.73 g, 3 mmol) was added . The reaction mixture was kept at reflux overnight. The mixture was then cooled, and the precitate filtered , washed with water to afford 0.5 g (86%) of **8** as a yellow solid

which was recrystallized using a DMF-water mixture, mp > 260°C. NMR (200 MHz , DMSO) δ: 3.6 (2H, s, CH_2), 7.2 to 7.55 (4H, m, phenyl), 12.15 (2H, brs, 2 x NH) . MS (EI) : m/z 200 (80%) , $M^{+\cdot}$. IR (KBr) cm^{-1} : 3475, NH ; 3250-2750 , NH ;1680 , 1650 , carbonyl.

2-Hydrazono-1,4-dihydroindeno[1,2-*b*]pyrazin-3-one (9)

A stirred solution of **8** (2 g, 0.01 mol) and 30% hydrazine monohydrate (6 mL, 0.1 mol) in 1-propanol (30 mL) was heated at reflux overnight. The mixture was then cooled, and **9** crystallized out . It was filtered, washed with water (3 x 50 mL) to give 0.45 g (21%) as a pale yellow solid, mp > 260°C (1-propanol). NMR (200 MHz , DMSO) δ : 3.6 (2H, s, CH_2), 4.5 (2H, brs, NH_2), 7.2 to 7.7(4H, m, phenyl), 8.5 (1H, brs, NH), 12.5(1H, brs, NH) . MS (DCI) : m/z 215 , MH^+. IR (KBr) cm^{-1}: 3415, 3290, NH_2 ; 3240 , NH ; 3150-2550 , NH ; 1650 , carbonyl.

Pathway A

Compounds (**1a-d**) were synthetized according to the Pathway A. Illustrative synthetic procedure is given for **1a** as a representative example .

5*H*,10*H*-Indeno[1,2-*e*]-1,2,4-triazolo[4,3-*a*]pyrazin-4-one (1a)

A stirred solution of **9** (0.45 g, 2 mmol) and trimethyl orthoformate (2 mL, 18 mmol) in xylene (10 mL) was heated at reflux for 8 h. The mixture was then cooled at rt, and **1a** crystallized out . It was filtered , washed with xylene (3 x 10 mL) and recrystallized from hot acetic acid, mp > 260°C. Finally **1a** (0.13 g) was obtained in a 21% yield. NMR (600 MHz , DMSO) δ : 4.05 (2H, s, H_{10}), 7.35 and 7.4 (2 x 1H, ddd, J= 8, 8 and 1.5, H_7 and H_8), 7.65 (1H , dd, J= 8 and 1.5, H_9); 7.9 (1H, dd, J= 8 and 1.5, H_6), 9.35 (1H, s, H_1), 12.5 (1H, brs, NH). Precise ^1H attributions were obtained thanks to accurate 1D nOe experiments performed at 300 MHz . Strong nOe enhancements were observed between H_{10} and H_9 ; H_{10} and H_1 in one hand , then between H_6 and NH in the other hand. MS (DCI) : m/z 225 , MH^+. IR (KBr) cm^{-1} : 3325, 3225-2700 , NH ; 1690 , carbonyl ; 1650, 1505, triazole ring breathing . *Anal.* Calcd for $C_{12}H_8N_4O$: C, 64.27 ; H, 3.60 ; N, 24.99. Found : C, 64.16 ; H, 3.41 ; N, 24.80.

Compounds (**1b**, **1c** and **1d**) were prepared according to the same procedure , starting from respectively : triethyl orthoacetate , triethyl orthopropionate and trimethyl orthovalerate in 27-29% yield . All the melting points were over 260°C (**1b** : from hot 0.1N NaOH then acidification with acetic acid until pH = 4-5 at rt, **1c** : from hot acetic acid, **1d** : from hot DMSO). **1b**, NMR (200 MHz, DMSO) δ : 2.8 (3H, s, methyl), 4.2 (2H, s, H_{10}), 7.35 (2H, m, H_7 and H_8), 7.6 (1H, dd, J= 8 and 1.5, H_9), 7.9 (1H, dd, J= 8 and 1.5, H_6), 12.4 (1H, brs, NH). MS (DCI) : m/z 239, MH^+. IR (KBr) cm^{-1}: 3225, NH ; 1690, CO ; 1645, 1505, triazole ring. *Anal.* Calcd for $C_{13}H_{10}N_4O$: C, 65.63 ; H, 4.23 ; N, 23.52. Found : C, 65.62 ; H, 4.37 ; N, 23.22 . **1c**, NMR (200 MHz, DMSO) δ: 1.5 (3H, t, J=7, methyl), 3.2 (2H, q, J=7, CH_2), 4.2 (2H, s, H_{10}), 7.4 (2H, m, H_7 and H_8), 7.6 (1H, brd, J= 8, H_9), 7.9 (1H, brd, J= 8, H_6), 12.5 (1H, b.s, NH). MS (DCI) : m/z 253 , MH^+ . IR (KBr) cm^{-1} : 3225, NH ; 1690, CO ; 1645, 1495 triazole ring. *Anal.* Calcd for $C_{14}H_{12}N_4O$: C, 66.65 ; H, 4.79 ; N, 22.21. Found : C, 66.53 ; H, 4.81 ; N, 22.37. **1d** , NMR (200 MHz, DMSO) δ :1 (3H, t, J=7, methyl), 1.5 (2H, m, CH_2), 1.9 (2H, m, CH_2), 3.2 (2H, t, J=7, CH_2), 4.25 (2H, s, H_{10}), 7.4 (2H, m, H_7 and H_8), 7.65 (1H, brd, J= 8, H_9), 7.9 (1H, brd, J= 8, H_6), 12.45 (1H, brs, NH). MS (DCI) : m/z 281 , MH^+. IR (KBr)cm^{-1} : 3250-2750, NH ; 1675, CO ; 1645,1495, triazole ring. *Anal.* Calcd for $C_{16}H_{16}N_4O$: C, 68.55 ; H, 5.75 ; N, 19.99. Found : C, 68.34 ; H, 5.61 ; N, 20.06.

Pathway B

2-Isobutylidenehydrazono-1,4-dihydroindeno[1,2-*b*]pyrazin-3-one (10a)

A solution of **9** (2.1 g, 0.01 mol), isobutyraldehyde (1.2 mL, 0.01 mol) in 1-propanol (36 mL) was heated at 70°C for 40 mn. The mixture was then cooled at rt, and **10a** which crystallized out was filtered, washed

with ether (3 x 30 mL) to afford 2 g (75%) as a cream solid, mp 242°C (1-propanol). NMR (300 MHz , DMSO) δ : 1.1 (6H, d, J= 7, methyl), 2.6 (1H, m, CH isopropyl), 3.7 (2H, s, H_{10}), 7.2 to 7.74 (4H, m, H_6 to H_9), 7.75 (1H, d, J= 6, NCH), 10.6 (1H, brs, NH), 12.8 (1H, brs, NH) . MS(DCI) : m/z 269 , MH^+. IR (KBr) cm^{-1} : 3325, 3225, NH ; 1660, CO ; 1555, C=N.

2-Cyclopropylidenehydrazino-1,4-dihydroindeno[1,2-*b*]pyrazin-3-one (10b)

10b was prepared according to the same procedure , starting from cyclopropylaldehyde in a 78% yield as a yellow solid, mp 262°C (1-propanol). NMR (300 MHz, DMSO) δ : 0.7 and 0.9 (4H, m, 2x CH_2 cyclopropyl), 1.75 (1H, m, CH cyclopropyl), 3.65 (2H, s, H_{10}), 7.3 to 7.45 (4H, m, H_6 to H_9), 7.8 (1H, d, J= 5, NCH), 11.04 (1H, brs, NH), 12.7 (1H, brs, NH). MS (DCI) : m/z 267 , MH^+.

1-Isopropyl-5*H*,10*H*-indeno[1,2-*e*]-1,2,4-triazolo[4,3-*a*]pyrazin-4-one (1e)

To a yellow stirred suspension of **10a** (2 g, 7 mmol) in propanol (36 mL), at rt, chloramine-T trihydrate (2.76 g, 9.8 mmol) was added. The mixture was then heated at reflux for 2 h and then cooled at rt. **1e** crystallized out and was filtered. It recrystallized from hot DMSO to afford 0.66 g (35%) as a pink solid, mp > 260°C. NMR (300 MHz , DMSO) δ : 1.4 (6H, d, J= 7, methyl), 3.6 (1H, m, CH isopropyl), 4.2 (2H, s, H_{10}), 7.45 (2H, m, H_7 and H_8), 7.6 (1H, brd, J= 8, H_9), 7.9 (1H, brd, J= 8, H_6), 12.5 (1H, brs, NH). MS (DCI) : m/z 267 , MH^+. IR (KBr) cm^{-1} : 3250-2750 , NH ; 1670 , CO ; 1495, 1485 , triazole. *Anal.* Calcd for $C_{15}H_{14}N_4O$: C ,67.65 ; H, 5.3 ; N, 21.04. Found : C, 67.63 ; H, 5.31 ; N, 20.89.

1-Cyclopropyl-5*H*,10*H*-indeno[1,2-*e*]-1,2,4-triazolo[4,3-*a*]pyrazin-4-one (1f)

1f was prepared according to the same procedure , starting from cyclopropanecarboxaldehyde , in a 30% overall yield, mp > 260°C (hot DMSO). NMR (200 MHz, DMSO) δ: 1.2 (4H, m, 2 x CH_2 cyclopropyl), 2.4 (1H, m, CH cyclopropyl), 4.3 (2H, s, H_{10}), 7.40 (2H, m, H_7 and H_8), 7.65 (1H, brd, J=8, H_9), 7.95 (1H, brd, J=8, H_6), 12.5 (1H, brs, NH). MS (DCI) : m/z 265, MH^+. IR (KBr) cm^{-1} : 3330 , NH ; 1680, CO ; 1655, 1505, triazole. *Anal.* Calcd for $C_{15}H_{12}N_4O$: C, 68.16 ; H, 4.57 ; N, 21.20. Found : C, 68.09 ; H, 4.75 ; N, 20.86.

Pathway C

1-Amino-5*H*,10*H*-indeno[1,2-*e*]-1,2,4-triazolo[4,3-*a*]pyrazin-4-one (1g)

To a solution of **9** (1.07 g, 5 mmol) in 1-propanol (20 mL), at rt, cyanogen bromide (0.6 g, 6 mmol) was added in a 2/5 methanol-water mixture (7 mL). The reaction mixture was heated at reflux for 6 h and then concentrated *in vacuo*. The residue was triturated with a saturated solution of $NaHCO_3$, filtered , washed with water (2 x 30 mL), acetone (3 x 20 mL) to give 1.1 g (92%) of **1g** as a purple solid, mp > 260°C. NMR (200 MHz , DMSO) δ : 4.2 (2H, s, H_{10}), 6.4 (2H, br.s, NH_2) 7.35 (2H, m, H_7 and H_8), 7.6 (1H, brd, J= 8, H_9), 7.9 (1H, brd, H_6), 12.2 (1H, brs, NH). MS (DCI) : m/z 240 , MH^+. IR (KBr) cm^{-1}: 3300 , 3200 , 3170 , NH ; 1695 , CO ;1650 , 1505 , triazole. *Anal.* Calcd for $C_{12}H_9N_5O$: C, 60.25 ; H, 3.79 ; N, 29.27. Found : C, 60.19 ; H, 3.43 ; N, 29.12 .

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