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Bioisosteres of 9-Carboxymethyl-4-oxo-imidazo[1,2-*a*]indeno-[1,2-*e*]pyrazin-2-carboxylic Acid Derivatives. Progress Towards Selective, Potent In Vivo AMPA Antagonists with Longer Durations of Action

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Abstract—A novel series of 2- and 9-disubstituted heterocyclic-fused 4-oxo-indeno[1,2-*e*]pyrazin derivatives was synthesized. One of them, the 9-(1*H*-tetrazol-5-ylmethyl)-4-oxo-5,10-dihydroimidazo[1,2-*a*]indeno[1,2-*e*]pyrazin-2-yl phosphonic acid **4i** exhibited a strong and a selective binding affinity for the AMPA receptor ($IC_{50} = 13$ nM) and demonstrated potent antagonist activity ($IC_{50} = 6$ nM) at the ionotropic AMPA receptor. This compound also displayed good anticonvulsant properties against electrically-induced convulsions after ip and iv administration with ED_{50} values between 0.8 and 1 mg/kg. Furthermore, a strong increase in potency was observed when given iv 3 h before test ($ED_{50} = 3.5$ instead of 25.6 mg/kg for the corresponding 9-carboxymethyl-2-carboxylic acid analogue). These data confirmed that there is an advantage in replacing the classical carboxy substituents by their bioisosteres such as tetrazole or phosphonic acid groups.

Evidence suggests that glutamate, the major fast excitatory neurotransmitter in the central nervous system, is involved in several neurodegenerative syndromes such as Huntington's and Alzheimer's diseases, as well as in brain ischemia and epilepsy.[1] These processes are mediated by NMDA, AMPA, kainate and metabotropic receptors which in turn each comprise several subclasses.[2] Blocking their activation is expected to have a neuroprotective effect.[3] AMPA antagonists have been obtained from various chemical series such as quinoxalines, heterocyclic-fused quinoxalinones, isatinoximes, quinazolines, quinolones and decahydroisoquinolines.[4] Representative examples are **NBQX**,[5] **YM90K**,[6] **YM872**,[7] **MPQX**,[8] (−)-**LY293558**[9] or **LY300164**[10] (Fig. 1). To date, **YM872** and **LY300164** (talampanel) are the most developed AMPA antagonists. These compounds have reached in Phase I/II and Phase II clinical trials for cerebrovascular ischemia, respectively.[11]

In the course of our efforts to optimize the glutamate receptor ligand imidazo[1,2-*a*]indeno[1,2-*e*]pyrazin-4-one **1**,[12] we have previously published on some original series of antagonists at the AMPA subtype of these receptors such as the spiro-imidazo[1,2-*a*]indeno[1,2-*e*]-pyrazin-4-ones (e.g., (+)-**2**)[13] that are active at both the glycine site of the NMDA and AMPA receptors, the 4-oxo-imidazo[1,2-*a*]indeno[1,2-*e*]pyrazin-2-carboxylic acid derivative **3**[14] and the more recently described 8- and 9-imidazo[1,2-*a*]indeno[1,2-*e*]pyrazin-9-acetic acids **4a** and **4b**[15] which display high and selective affinity at AMPA receptors (Table 1).

Encouraged by these results, we have now tried replacing the two carboxylic moieties of **4a** and **4b** in order to investigate further the structure–activity relationships (SARs) in this family. Of particular interest was the

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attempt to introduce a tetrazole ring and a phosphonic acid group which are well known to be bioisosteres of carboxylic acid functions[16] and have led in several cases to enhancements of potency, selectivity and/or bioavailability.[17]

In this study, we describe the synthesis and the binding properties of 4-oxo-imidazo[1,2-*a*]indeno[1,2-*e*]pyrazines **4c**–**o**.[18a,b] We also report their anticonvulsant effects in vivo, when administered by ip and iv routes, to normal mice submitted to an electric shock (MES). The influence of bioisosteric replacement of carboxylic acids in positions 2 and 9 of parent compounds **4a** and **4b** is particularly studied with the objective of obtaining potent AMPA antagonists with long durations of action.

Chemistry

The 4-oxo-imidazo[1,2-*a*]indeno[1,2-*e*]pyrazines **4c**–**o** were prepared following a four- or a five-step synthesis as outlined in Scheme 1. The 2-bromo indanones **6** were obtained from indanones **5**[19] using either bromide or pyridinium perbromide monohydrate with a 36–100% overall yield. Subsequent, regioselective condensation of 6 with the various 4-substituted-2-ethoxycarbonyl-imidazoles **9**–**11**[20] and **12**–**15**,[21,24] in the presence of potassium carbonate at reflux in acetone, afforded analogues of type **7** directly with low to excellent yields (25–100%) or following simple hydrolysis and amidification protocols. Thus, the methylsulfonamide and phenylsulfonamide analogues of **7** were obtained (38–52% yield). Treatment of **7** with ammonium acetate in glacial acetic acid or 5 N NH_3/MeOH, at reflux, led to the corresponding 4-oxo-imidazo[1,2-*a*]indeno[1,2-*e*]pyrazines derivatives **8** with moderate yield (30–60%). Finally, the synthesis of **4c**,**d**,**g**–**k**,[22]**m**–**o** was achieved by the hydrolysis of the corresponding 4-oxo-imidazo[1,2-*a*]indeno[1,2-*e*]pyrazine derivatives **8c**,**d**,**g**–**k**,**m**–**o** using either acidic (HBr, HCl) or basic conditions (NaOH) followed by the action of HCl (40–80% yield). The expected compounds **4e** and **4f** were readily saponified (NaOH) with 60 and

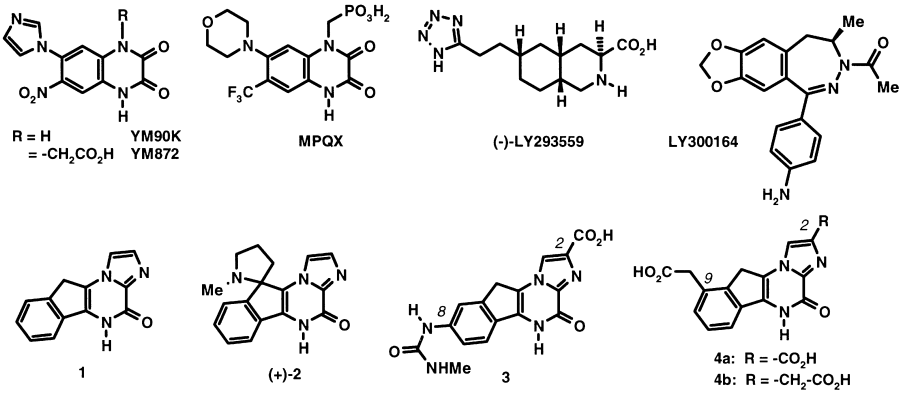


Figure 1.

Table 1. Binding studies and anticonvulsant profile by ip and iv route of **1**, **4a**–**o**, **NBQX**, **YM90K** and **(−)-LY293558**

Compound	Receptor affinity IC_{50}[a] nM		Anticonvulsant activity MES ED_{50}[b] mg/kg	
	AMPA	NMDA/glycine	ip	iv
1	760	3000	62	—
4a	18	7200	1.2	0.5
4b	4	2100	2	0.5
4c	15	537	2.3	2.0
4d	586	>10,000	5.6	—
4e	189	328	10	5
4f	235	1200	—	—
4g	139	2000	—	—
4h	150	>10,000	3.5	2.9
4i	13	2360	1	0.8
4j	147	>10,000	4.7	2.5
4k	30	>10,000	2.2	3.8
4l	31	1600	1.9	—
4m	12	5800	5	5
4n	40	7200	8.6	—
4o	100	6100	—	—
NBQX	140	>10,000	36	—
YM90K	350	10,400	12	12
(−)-LY293558	600	>10,000	4	3.4

[a]IC_{50} values are mean of at least three determinations, each with at least three concentrations of tested compound in triplicate.
[b]ED_{50} values are defined as the dose which protected 50% of the animals from a tonic convulsion (six male CD1 mice/dose of compound, with at least three doses compared to a group receiving vehicle alone, pretreatment time by ip route: 30 min; iv route: 5 min, vehicle for ip: 1% Tween-80 in water, vehicle for iv: saline.

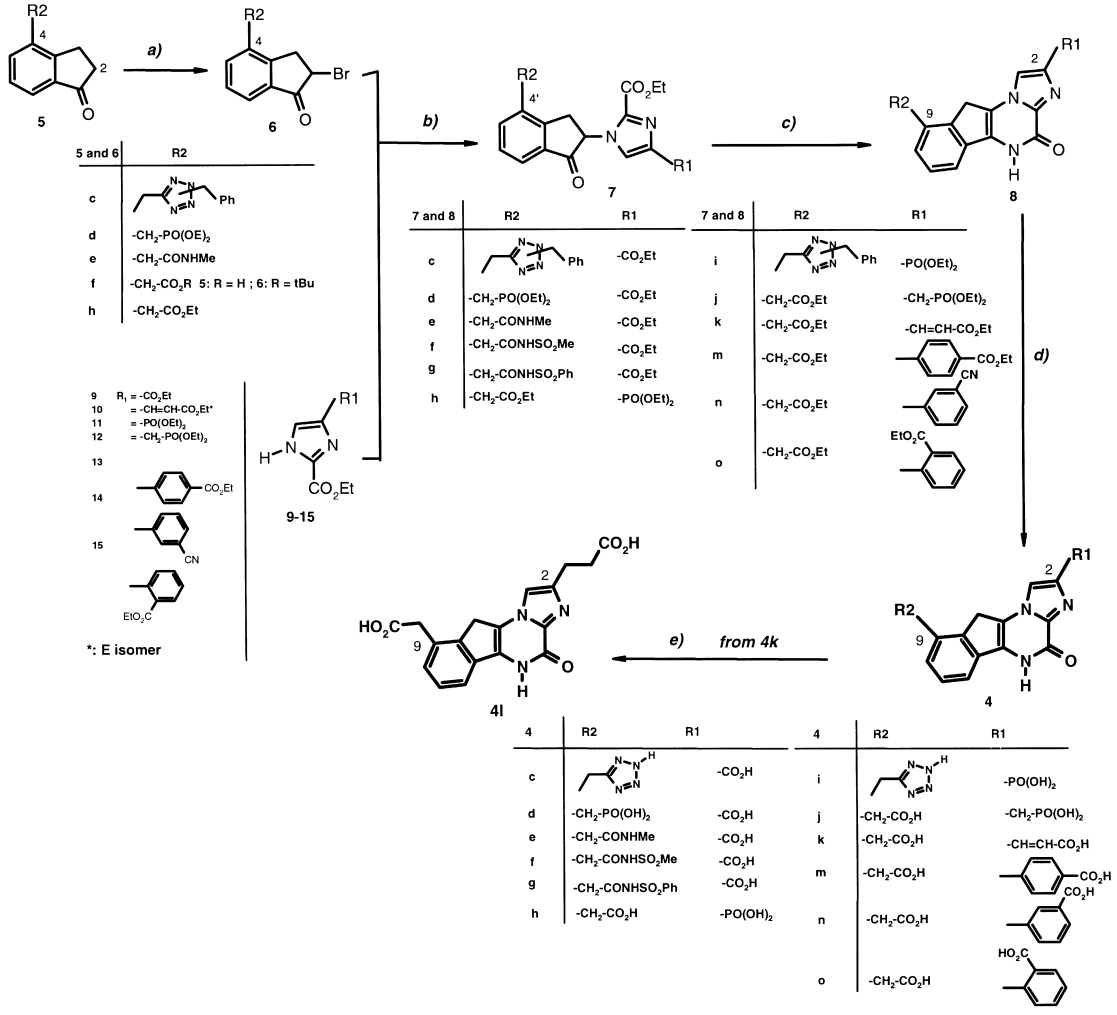
90% yields, respectively. Hydrogenation of **4k** in the presence of a catalytic amount of Pd/C (10%) led to **4l** with a 50% yield.

Biological Activity and SARs

In vitro studies

The binding affinities for AMPA and glycine/NMDA receptors were evaluated in in vitro binding assays using [^{3}H]-AMPA[25] and [^{3}H]-5,7-dichlorokynurenate ([^{3}H]-DCKA)[26] as selective [^{3}H]-ligands on rat cortical membrane preparations. Results for compounds **1**, **4a–o**, **NBQX**, **YM90K** and **(−)-LY293558** are reported in Table 1.

On the basis of these binding data, the following SARs could be highlighted: *in position 9*, replacement of the carboxylic acid of **4a** by several known bioisosteres, that is tetrazole (**4c**), phosphonic acid (**4d**), *N*-methylcarboxamide (**4e**), *N*-methylsulfonylcarboxamide (**4f**) or *N*-phenylsulfonylcarboxamide (**4g**), was only successful for compound **4c** by the introduction of the tetrazolyl moiety. The AMPA binding affinity was retained ($IC_{50} = 15$ nM) but about a 10-fold decrease of selectivity versus the glycine/NMDA binding site was observed. The other isosteric replacements led to more dramatic changes reducing the potency of the AMPA ligands by a factor of 8–32. *In position 2*, replacement of the carboxy groups of **4a** and **4b** was performed with two complementary objectives: either a bioisosteric modification as in position 9 in order to get improvements of the pharmacodynamic profile, or a further exploration of



Scheme 1. Synthesis of **4c–o**. Reagents and conditions: (a) **6c,e,h**: Br_2, CH_2Cl_2, rt, 1–5 h, 88–100%; **6d**: pyridinium perbromide monohydrate, 50 °C, 0.25 h, 77%; **6f**: AcOH, HBr (47%), Br_2, rt, 1 h, 84% then PhMe, *N,N*-dimethylformamide di-*tert*-butyl acetal, 80 °C, 10 min, 36%; (b) K_2CO_3, acetone, reflux, 1–4 h, 27–100%, **7c,d**: **9**, **7h,i**: **11**, **7j**: **12**, **7k**: **10**, **7m**: **13**, **7n**: **14**, **7o**: **15**; **7e**: **9**, K_2CO_3, 18-crown-6, acetone, reflux, 2 h, 26%; **7g**: (1) **9**, K_2CO_3, acetone, reflux, 4 h, 90%; (2) 6 N HCl, dioxane, 89%; (3) CDI, THF, rt, 1.5 h then $PhSO_2NH_2$, NaH, THF, rt, 1 h, 65%; **7f**: **9**, K_2CO_3, acetone, reflux, 4 h, 90% then 6 N HCl, dioxane, 89% then CDI, THF, rt, 0.5 h followed reflux, 0.5 h then $MeSO_2NH_2$, DBU, THF, rt, 18 h, 47%; (c) **8c–h,j,k,m–o**: $AcONH_4$, AcOH, reflux, 1–7 h, 29–61%; **8i**: 5 N NH_3/MeOH, reflux, 16 h then $AcONH_4$, AcOH, reflux, 16 h, 43%; (d) **4c,d**, **4i·HBr**: HBr (30–47%), 3–20 h, reflux, 42–62% **4e·3H$_2$O**, **4f·di-sodium salt**: 1 N NaOH, H_2O, dioxane, rt, 6 h, 63–92%; **4g**: 1 N NaOH, H_2O, dioxane, rt, 20 h then 1 N HCl, rt, 2 h, 49%; **4h,j**, **4m·HCl**, **4n·HCl**: 6 N HCl, rt, 2–16h, 66–79%; **4k·HCl**: cHCl/AcOH, reflux, 48 h, 54%; **4o**: 12 N HCl, reflux, 64 h, 54%; (e) **4l**: **4k**, H_2 (pressure: 73.5 psi), 0.3 N NaOH, Pd/C (10%), rt, 12 h then 1 N HCl until pH = 7, 50%.

the SAR in this position by lengthening and/or constraining the carboxyalkyl-like chain. The introduction of a phosphonic acid as a substitute for the carboxylic acid of **4a** and **4b** induced in both cases a lower potency leading to compounds with moderate affinities (**4h** and **4j**, IC_{50} = 147–150 nM). Pursuing the lengthening of the carboxyalkyl chain by the introduction of either a carboxyethyl group or the unsaturated *E*-carboxylidene moiety decreased the potency for the AMPA receptor by about 10-fold (**4l** and **4k** versus **4b**). We next turned our attention to explore the effects of introducing 2-, 3-, or 4-carboxyphenyl moieties. Moving the carboxylic acid around the phenyl ring from position 2 to positions 3 and 4 (**4m–o**) increased the AMPA affinity with IC_{50}'s as low as 12, 40 and 100 nM, respectively. Interestingly, the most potent derivative **4m** demonstrated the same level of AMPA binding potency and selectivity against the glycine site of the NMDA receptor as the parent carboxylic acid **4a**, thus showing room for possible drastic modifications in position 2 of this series of AMPA ligands.

In comparison with **NBQX**, **YM90K** and **(–)-LY293558**, the fused 2,9-disubstituted-4,10-dihydro-4-oxo-4*H*-imidazo[1,2-*a*]indeno[1,2-*e*]pyrazines **4c,i,m** exhibited a 10- to 40-fold higher potency at the AMPA receptor while they retained a good selectivity versus the glycine site of the NMDA receptor (between 36- and 480-fold). In addition, **4c,i,m** were about 50-fold more potent for the AMPA receptor than the unsubstituted derivative **1**.

The functional activity of **4i** at AMPA receptors was determined using kainate-evoked currents in *Xenopus* oocytes injected with human recombinant GluR1 + GluR2 mRNA. The potency of this ligand at AMPA receptors was examined using current response analysis as previously described.[27] Compound **4i** antagonized kainate-induced responses in a concentration-dependent manner showing an IC_{50} value of 6 nM (Fig. 2) versus 260 and 230 nM (rat cortex mRNA) for **YM90K** and **(–)-LY293558**, respectively.

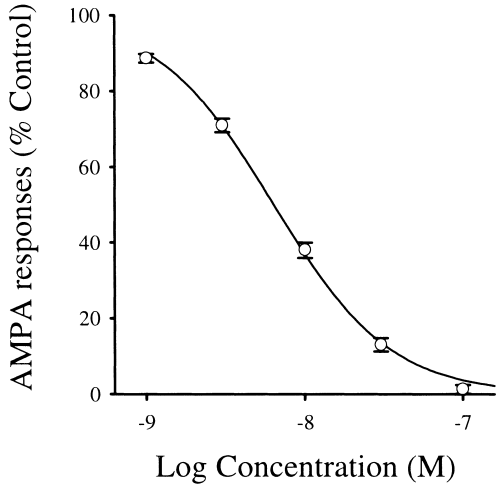


Figure 2. Antagonist activity of compound **4i** against functional responses mediated by AMPA receptors in voltage clamped oocytes. Data are mean±SD response of three oocytes in the presence of the indicated concentration of **4i**.

In vivo studies

Compounds **4c–e,h–n** demonstrated moderate to good in vivo activities against MES-induced convulsions[28] in normal mice following ip (30 min before challenge) or iv administration (5 min before challenge) with ED_{50} values between 0.8 and 8.6 mg/kg. Among these compounds, **4i** displayed the strongest anticonvulsant properties with an ED_{50} of 1 and 0.8 mg/kg by ip and iv route, respectively.

The duration of action of several of the most potent compounds in this series (**4a–c,e,h–k,m**) was studied in the MES test (pre-treatment time: 3 h) following iv administration in the mouse. As shown in Table 2, the compounds **4i** and **4h** demonstrated long durations of action with ED_{50}'s of 3.5 mg/kg. Compared to the parent compound **4a**, replacement of the carboxy group by a phosphonic acid *in position 2* (compound **4h**) led to a dramatic increase of potency after a 3 h pre-treatment (ED_{50} = 3.5 versus 25.6 mg/kg iv). This combines with about a 10-fold decrease of affinity for the AMPA receptor, thus the improvement of in vivo potency is impressive; it suggests the superiority of the phosphonic over the carboxylic moiety for in vivo activity and a long duration of action, in this series. This superiority is also evident by comparing **4j** and **4b**: despite a 36-fold lower binding potency, the phosphonic analogue **4j** only displayed a 2-fold decrease of anticonvulsant activity after 30 min (ip) or 5 min (iv) and similar protective effect administered iv 3 h before challenge to the carboxylic derivative **4b**. The other modifications in position 2 were less critical leading to compounds with similar in vivo potency and duration of action to the parent carboxylic acids (**4k,m** versus **4a,b**). *In position 9*, replacement of the carboxymethyl group by a 1*H*-tetrazol-5-yl moiety while it did not induce any significant change in **4c** compared to **4a**, but when combined with the introduction of a phosphonic acid in position 2 as in **4i** versus **4h**, both in vitro and in vivo potency enhancements were observed giving the very potent and selective AMPA antagonist **4i** with a duration of action lasting at least 3 h. This contrasts with **YM90K** where, 3 h post-administration, the efficacious dose exceeded 40 mg/kg. The iv administration of **4i** was also largely facilitated by its high solubility in saline solution (~10 g/L).

Table 2. Duration of action of compounds **4a–c,e,h–k,m** and **YM90K** in the mouse (iv, 3 h post-administration)

Compound	Anticonvulsant activity ED_{50}[a] mg/kg
4a	25.6
4b	28
4c	In. 40
4e	>20
4h	3.5
4i	3.5
4j	22.4
4k	25.6
4m	15
YM90K	>40

[a]ED_{50} values are defined as the dose which protected 50% of the animals from a tonic convulsion (six male CD1 mice/dose of compound, with at least three doses compared to a group receiving vehicle alone (vehicle: saline).

In conclusion, this study reports a novel series of 2- and 9-disubstituted heterocyclic-fused 4-oxo-indeno[1,2-*e*]-pyrazines. The best biological activities were obtained with a phosphonic acid group in position 2 and either a carboxymethyl or a (1*H*-tretrazol-5-yl) methyl group in position 9 of the 5*H*,10*H*-imidazo[1,2-*a*]indeno[1,2-*e*]-pyrazine-4-one ring. Compound **4i** possesses one of the highest affinities for the AMPA receptor ($IC_{50} = 13$ nM), a good selectivity against the glycine site of the NMDA receptor (~180-fold) and also exhibits potent anti-convulsant effects following ip and iv administration at doses below 1 mg/kg with a long duration of action compared to the carboxylic acid analogues **4a** and **4b**. In addition, **4i** exhibits very potent antagonist intrinsic activity against AMPA receptor-mediated responses in *Xenopus* oocytes ($IC_{50} = 6$ nM). This compound certainly represents one of the very few soluble and long lasting AMPA antagonists reported to date. Therefore, in the imidazo[1,2-*a*]indeno[1,2-*e*]pyrazin-4-one series, it seems to be advantageous from a pharmacodynamic point of view to replace the classical carboxy substituents by their bioisosteres such as a tetrazole or a phosphonic acid group as far as this chemical modification is tolerated by the receptor site.

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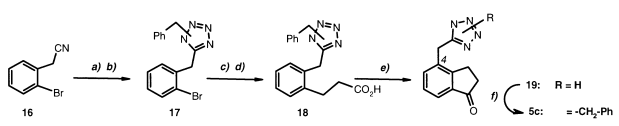
References and Notes

1. (a) For recent reviews, see: Satkowski, M.; Attwell, D. *Trends Neurosci*. **1994**, *17*, 359. (b) Danysz, W.; Parsons, C. G.; Bresink, I.; Quack, G. *Drug News Perspect*. **1995**, *8*, 261. (c) Doble, A. *Pharmacol. Ther*. **1999**, *81*, 163 and references cited therein.
2. Nakanishi, S. *Science* **1992**, *258*, 597 and references cited therein.
3. For a recent review, see: *Nature* **1999**, *399*(Suppl), and references cited therein.
4. For a recent review, see: Chimirri, A.; Gitto, R.; Zappalà, M. *Exp. Opin. Ther. Patents* **1999**, *9*, 557 and references cited therein.
5. Sheardown, M. J.; Nielsen, E. O.; Hansen, A. J.; Jacobsen, P.; Honore, T. *Science* **1990**, *247*, 571.
6. Ohmori, J.; Sakamoto, S.; Kubota, H.; Shimizu-Sasamata, M.; Okada, M.; Kawasaki, S.; Hidaka, K.; Togami, J.; Furuya, T.; Murase, K. *J. Med. Chem*. **1994**, *37*, 467.
7. Habert, A.; Takahashi, M.; Yamaguchi, T.; Hjelstuen, M.; Haraldseth, O. *Brain Res*. **1998**, *811*, 63.
8. Turski, L.; Huth, A.; Scheardown, M.; Wiegand, F.; Jacobsen, P.; Ottow, E. *Proc. Natl. Acad. Sci. U.S.A*. **1998**, *95*, 10960.
9. Ornstein, P. L.; Arnold, M. B.; Augenstein, N. K. *J. Med. Chem*. **1993**, *36*, 2046.
10. Anderson, B. A.; Harn, N. K.; Hansen, M. M.; Harkness, A. R.; Lodge, D.; Leander, J. D. *Bioorg. Med. Chem. Lett*. **1999**, *9*, 1953.
11. (a) Anderson, B. A.; Harn, N. K.; Hansen, M. M.; Harkness, A. R.; Lodge, D.; Leander, J. D. *Bioorg. Med. Chem. Lett*. **1999**, *9*, 1953. (b) Wojciech, D. *Drugs* **2000**, *3*, 84 and references cited therein.
12. Mignani, S.; Aloup, J.-C.; Blanchard, J.-C.; Bohme, G. A.; Boireau, A.; Damour, D.; Debono, M. W.; Dubroeucq, M.-C.; Genevois-Borella, A.; Imperato, A.; Jimonet, P.; Pratt, J.; Randle, J. C. R.; Reibaud, M.; Ribeill, Y.; Stutzmann, J.-M. *Drug. Dev. Res*. **1999**, *48*, 121.
13. Jimonet, P.; Boireau, A.; Chevé, M.; Damour, D.; Genevois-Borella, A.; Imperato, A.; Pratt, J.; Randle, J. C. R.; Ribeill, Y.; Stutzmann, J.-M.; Mignani, S. *Bioorg. Med. Chem. Lett*. **1999**, *9*, 2921.
14. Stutzmann, J.-M.; Bohme, G. A.; Boireau, A.; Damour, D.; Debono, M. W.; Genevois-Borella, A.; Imperato, A.; Jimonet, P.; Pratt, J.; Randle, J. C. R.; Ribeill, Y.; Vuilhorgne, M.; Mignani, S. *Bioorg. Med. Chem. Lett*. **2000**, *10*, 1133.
15. Pratt, J.; Jimonet, P.; Bohme, G. A.; Boireau, A.; Damour, D.; Debono, M. W.; Genevois-Borella, A.; Randle, J. C. R.; Ribeill, Y.; Stutzmann, J.-M.; Vuilhorgne, M.; Mignani, S. *Bioorg. Med. Chem. Lett*. **2000**, *10*, 2749.
16. Lipinski, C. A. *Annu. Rep. Med. Chem*. **1986**, *27*, 283 and references cited therein.
17. (a) For examples, see: Auberson, Y. P.; Acklin, P.; Bischoff, S.; Moretti, R.; Ofner, S.; Schutz, M.; Veenstra, S. *Bioorg. Med. Chem. Lett*. **1999**, *9*, 249. (b) Marshall, W. S.; Goodson, T.; Cullinan, G. J.; Swanson-Bean, D.; Haisch, K. D.; Rinkema, L. E.; Fleisch, J. H. *J. Med. Chem*. **1987**, *30*, 682. (c) Kraus, J. L. *Pharmacol. Res. Commun*. **1983**, *15*, 183.
18. (a) All the new compounds described herein have been fully characterized using ^{1}H NMR, IR and mass spectroscopies, and have given satisfactory elemental analyses (C, H, N). As examples, data obtained for the most potent in vivo compounds **4i** and **4k** are reported in ref 22. (b) Aloup, J.-C.; Audiau, F.; Barreau, M.; Damour, D.; Genevois-Borella, A.; Hardy, J.-C.; Jimonet, P.; Manfré, F.; Mignani, S.; Bouquerel, J.-C.; Nemecek, P.; Ribeill, Y. Patent applications WO96/31511; *Chem. Abstr. 126*:8136 and WO97/25328; *Chem. Abstr. 127*:176439.
19. (a) The indanone **5c** was prepared in a six-step pathway from the commercially available 2-bromophenyl-acetonitrile **16** according to the sequence outlined in Scheme 2. No attempt has been conducted to locate the position of the benzyl group attached to the tetrazole ring of **17**, **18** and **5c**. (b) The 4-diethylphosphonomethyl-indanone **5d** was prepared using an Arbuzov–Michaelis reaction by the condensation of triethylphosphite with (4-bromomethyl)indanone[23] in xylene at reflux (8 h) with 63% yield. (c) The 4-carboxymethylindanone **5f** was obtained in a three-step synthesis from 2-bromophenylacetic acid via a Heck reaction with acrylic acid [($Pd(OAc)_2$/tri-*o*-tolylphosphine)], followed by hydrogenation of the double bound (Pd/C) and finally a Friedel–Craft cyclization (concd H_2SO_4) with 11% overall yield. Esterification of **5f** (EtOH/ClCOCOCl) gave **5h** with 57% yield,

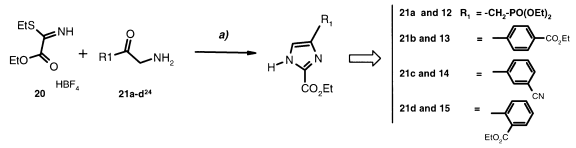


Scheme 2. Synthesis of **5c**: (a) NaN_3, NH_4Cl, DMF, 100 °C, 6 h, 83.5%; (b) $BrCH_2Ph$, K_2CO_3, acetone, reflux, 5 h, 100%; (c) acrylic acid, $Pd(OAc)_2$, Et_3N, tri-*o*-tolylphosphine, 100 °C, 16 h, 92%; (d) H_2 (pressure: 22 psi), Pd/C (10%), NaOH/H_2O, 1.5 h, 84%; (e) H_2SO_4 (95%), 100 °C, 0.5 h, 64%; (f) $BrCH_2Ph$, K_2CO_3, acetone, reflux, 5 h, 100%.

whereas the action of the methylamine with **5f** (CDI/THF) afforded **5e** with 75% yield (Structure, see Scheme 1).

20. **9**: Branco, P. S.; Prabhakar, S.; Lobo, A. M.; Williams, D. *Tetrahedron* **1992**, *48*, 6335. **10**: 4-(3-Ethoxy-3-oxo-1-propenyl)-imidazole-2-carboxylate (**10**) was prepared in three-step synthesis from commercially available 2,5-dihydro-2,5-dimethoxy furfurylamine via a Cornforth–Huang-cyclization reaction with 17.5% overall yield (Vuilhorgne, M.; Bouquerel, J.; Mignani, S. *Syn. Lett*. **2000**, submitted for publication). **11**: 2-Ethoxycarbonyl-imidazole-4-phosphonate (**11**) was prepared in one-step synthesis by the condensation of hydroxyiminoglycine ethyl ester (Gregory, G. I.; Seale, P. W.; Warburton, W. K.; Wilson, M. J. *J. Chem. Soc., Perkin Trans. 1* **1973**, 47) with diethyl ethylphosphonate (Daniel, T.; McMils, M. C.; Chamberlin, A., Cotman, C. W. *Brain Res*. 278, **1983**, 137) with 17% yield, Canton, T.; Böhme, G. A.; Boireau, A.; Mignani, S.; Jimonet, P.; Vuilhorgne, M.; Debono, M.-W.; Le Guern, S.; Laville, M.; Briet, D.; Roux, M.; Stutzmann, J.-M.; Pratt, P. *J. Pharmacol. Exp. Ther*. **2000**, submited for publication.

21. The 2-ethoxycarbonyl imidazole derivatives **12**–**15** were easily prepared in a one-step synthesis with 27–73% yields (Scheme 3).



Scheme 3. Synthesis of **12**–**15**. Reagents and conditions: (a) AcOH, AcONa, 95 °C, 3–3.5 h, **12**: 69%, **13**: 73%, **14**: 53.5%, **15**: 27%.

22. **4i·HBr** (RPR 121879): NMR (250 MHz, DMSO) δ: 4.1 (2H, s, H_{10}), 4.45 (2H, s, CH_2), 7.2 (1H, dd, $J=8$ and 1.5 Hz, H_8), 7.45 (1H, t, $J=8$ Hz, H_7), 7.8 (1H, dd, $J=8$ and 1.5 Hz, H_6), 8.2 (1H, s, H_1), 12.45 (1H, br.s, H_5). Attributions were secured thanks to NOE observation. Strong enhancements were obtained between H_1 and H_{10} on the one hand, and between the methylene group attached to the tetrazole and H_8, H_{10} on the other. MS (FAB, Gly/SGly): m/z 386 (MH^+). IR (KBr) cm^{-1}: 3250–2100, 1695, 1210, 975, 925. Elemental analysis: % calcd C 38.65, H 2.81, N 21.03; found C 38.45, H 2.8, N 20.93. **4k·HCl** (RPR 127759): NMR (250 MHz, DMSO) δ: 3.8 (2H, s, CH_2), 4 (2H, s, H_{10}), 6.65 (1H, d, $J=16$ Hz, CH=CH, *trans*), 7.25 (1H, dd, $J=8$ and 1.5 Hz, H_8), 7.4 (1H, t, $J=8$ Hz, H_7), 7.6 (1H, d, $J=16$ Hz, CH=CH, *trans*), 7.85 (1H, dd, $J=8$ and 1.5 Hz, H_6), 8.45 (1H, s, H_1), 12.7 (1H, br.s, H_5). Stereochemistry of the double bond (*E*) was easily deduced from the value ($J=16$ Hz) of the vicinal coupling constant while the expected NOEs were observed between the CH_2COOH and H_8, H_{10} on the one hand and between H_1, H_{10} and the CH=CH protons on the other. MS (CI, NH_3): m/z 352 (MH^+). IR (KBr) cm^{-1}: 3380, 3200–2300, 1695, 1680. Elemental analysis: % calcd C 55.75, H 3.64, N 10.84; found C 55.7, H 3.84, N 10.8.

23. Nakada, Y.; Ohno, S.; Yoshimoto, M.; Yura, Y. *Agric. Biol. Chem*. **1978**, *42*, 1365.

24. **21a**: Verbruggen, C.; De Craeker, S.; Rajan, P.; Jiao, X.-Y.; Borloo, M.; Smith, K.; Fairlamb, A. H.; Haemers, A. *Bioorg. Med. Chem. Lett*. **1996**, *6*, 253. **21b** and **21d** were prepared in a two-step synthesis from the corresponding ethyl 4-bromoacetylbenzoate (Desideri, N.; Conti, C.; Sestili, I. M.; Tomao, P.; Stein, M. L.; Orsi, N. *Antiviral Chem. Chemother*. **1992**, *3*, 195) and ethyl 2-bromoacetylbenzoate (Viti, G.; Giannotti, D.; Nannicini, R.; Ricci, R.; Pestellini, V. *J. Heterocycl. Chem*. **1991**, *28*, 379) by the condensation with diformylimide sodium salt (MeCN, 80 °C, 3–16 h) followed by the action of 5% solution of HCl in ethanol (rt, 3 h) with 33 and 50% overall yield, respectively. **21c**: Pratesi, P.; Grana, E.; Villa, L. *Farmaco* **1973**, *28*, 753.

25. Honoré, T.; Drejer, J. *J. Neurochem*. **1988**, *51*, 457.

26. Canton, T.; Doble, A.; Miquet, J.-M.; Jimonet, P.; Blanchard, J.-C. *J. Pharm. Pharmacol*. **1992**, *44*, 812.

27. Debono, M. W.; Le Guern, J.; Canton, T.; Doble, A.; Pradier, L. *Eur. J. Pharmacol*. **1993**, *235*, 283.

28. Swinyard, E. A.; Brown, W. C.; Goodmann, L. S. *J. Pharmacol. Exp. Ther*. **1952**, *106*, 319.