ISSN 1070-3632, Russian Journal of General Chemistry, 2015, Vol. 85, No. 6, pp. 1452–1455. © Pleiades Publishing, Ltd., 2015.
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Cycloalkaneindoles with 2-Trifluoromethylimidazo[1,2-*a*]pyridin-6-yl Fragment

V. B. Sokolov, A. Yu. Aksinenko, T. A. Epishina, T. V. Goreva, A. V. Gabrel'yan, O. A. Dranii, V. V. Grigor'ev, and S. O. Bachurin

Institute of Physiologically Active Compounds, Russian Academy of Sciences, Severnyi pr. 1, Chernogolovka, Moscow oblast, 142432 Russia
e-mail: alaks@ipac.ac.ru

Received March 17, 2015

Abstract—Modification of biologically active cycloalkaneindoles by incorporation of a 2-trifluoromethylimidazo[1,2-*a*]pyridin-6-yl fragment has been proposed and performed via the interaction with 3-fluoro-2-trifluoromethylimidazo[1,2-*a*]pyridines in the presence of potassium hydroxide. The action of the prepared compounds on neuronal NMDA receptors has been studied by means of radioligand binding.

Keywords: cycloalkaneindole, 2-trifluoromethylimidazo[1,2-*a*]pyridine, radioligand binding, neuronal NMDA receptor

DOI: 10.1134/S1070363215060158

The substituted gamma carbolines, for example, a Russian drug Diberon [1, 2] and its 5-substituted analogs (including those with fluorine-containing groups in the position *5* [3, 4]) have been recognized as promising medicinal agents for treatment of chronic neurodegenerative diseases. Besides the gamma carboline derivatives [1–6], their tetrahydrocarbazole analogs containing the 2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indole scaffold as well have been suggested as neuroprotective drugs; such compounds may act as antagonists of the 5-HT_6 subtype of serotonin receptors [7] or inhibitors of peroxide oxidation of lipids [8], they exhibit the enhanced affinity towards NMDA receptors [9]. We have earlier demonstrated that introduction of the 2-trifluoromethylimidazo[1,2-*a*]pyridin-3-yl fragment into the gamma carbolines structure significantly improves their biological activity as compared to that of the parent compounds [5].

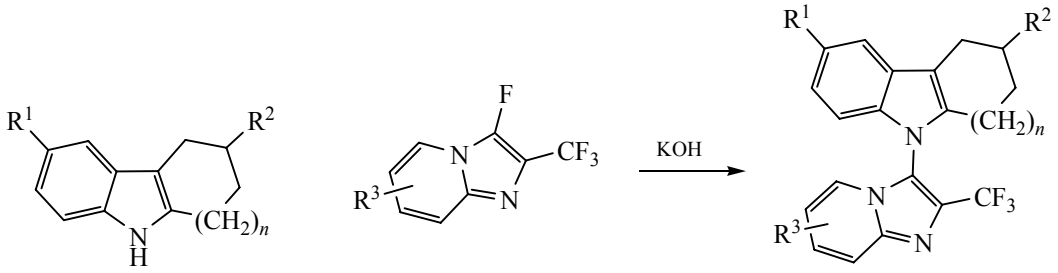
This work aimed at preparation and study of physiological activity of the previously unknown 2-trifluoromethylimidazo[1,2-*a*]pyridin-3-yl-2,3,4,9-tetrahydro-1*H*-carbazoles (**IIIa**–**IIIf**) and 2-trifluoromethylimidazo[1,2-*a*]pyridin-3-yl-2-fluoro-5,6,7,8,9-hexahydrocyclohepta[*b*]indoles (**IIIg**, **IIIh**).

It was shown that heating for 2 h an equimolar mixture of a cycloalkaneindole (**Ia–Ie**) and a 3-fluoro-2-trifluoromethylimidazo[1,2-*a*]pyridine (**IIa**–**IIc**) in DMF at 110°C in the presence of KOH afforded the corresponding 2-trifluoromethylimidazo[1,2-*a*]pyridin-3-yl-2,3,4,9-tetrahydro-1*H*-carbazoles (**IIIa**–**IIIf**) and 2-trifluoromethylimidazo[1,2-*a*]pyridin-3-yl-2-fluoro-5,6,7,8,9-hexahydrocyclohepta[*b*]indoles (**IIIg**, **IIIh**) in yields of 65–77% (Scheme 1).

The indoles **IIIa**–**IIIh** were solid crystalline substances; their composition and structure were confirmed by the data of elemental analysis and as ^{1}H and ^{19}F NMR spectra (Tables 1 and 2). In particular, the ^{19}F NMR spectra contained the fluorine signals at 15.2–15.6 ppm characteristic of the trifluoromethyl group at the double bond or at the aromatic ring, in the most of the products (**IIIb**, **IIIc, IIIe–IIIg**) two singlet signals were observed with Δ_δ of 0.07–0.08 ppm and the integral intensities ratio of 1 : 0.4 (**IIIf**) to 1 : 0.9 (**IIIg**), corresponding likely to a pair of rotamers.

Binding of compounds **IIIa**–**IIIh** at different modulating fragments of NMDA receptors was investigated by the radioligand method. The competitive binding of the compounds and [^{3}H]MK-801 (Dizocilpine) was used to determined the ability of the compounds to interact with the whole pool of the NMDA receptors, whereas the competition with [^{3}H] Ifenprodil reflected the compounds binding with the

Scheme 1.



Ia–Ie **IIa–IIc** **IIIa–IIIh**

I, $R^1 = CH_3$, $R^2 = H$, $n = 1$ (**a**); $R^1 = CH_3$, $R^2 = CH_3$, $n = 1$ (**b**); $R^1 = F$, $R^2 = H$, $n = 1$ (**c**); $R^1 = F$, $R^2 = CH_3$, $n = 1$ (**d**); $R^1 = F$, $R^2 = H$, $n = 2$ (**e**); **II**, $R^3 = 5\text{-}CH_3$ (**a**), $6\text{-}CH_3$ (**b**), $8\text{-}CH_3$ (**c**); **III**, $R^1 = CH_3$, $R^2 = H$, $R^3 = 6\text{-}CH_3$, $n = 1$ (**a**); $R^1 = CH_3$, $R^2 = CH_3$, $R^3 = 5\text{-}CH_3$, $n = 1$ (**b**); $R^1 = CH_3$, $R^2 = CH_3$, $R^3 = 8\text{-}CH_3$, $n = 1$ (**c**); $R^1 = F$, $R^2 = H$, $R^3 = 6\text{-}CH_3$, $n = 1$ (**d**); $R^1 = F$, $R^2 = CH_3$, $R^3 = 5\text{-}CH_3$, $n = 1$ (**e**); $R^1 = F$, $R^2 = CH_3$, $R^3 = 8\text{-}CH_3$, $n = 1$ (**f**); $R^1 = F$, $R^2 = H$, $R^2 = 6\text{-}CH_3$, $n = 2$ (**g**); $R^1 = F$, $R^2 = H$, $R^3 = 8\text{-}CH_3$, $n = 2$ (**h**).

NMDA receptors containing the NR2B subunits. The latter property is of special interest, since antagonists of the NR2B-containing NMDA receptors are known to exhibit significant therapeutic potential. The compounds were tested at the concentration range of 10^{-9}–10^{-4} mol/L *in vitro*, the results are collected in Table 3.

The obtained results evidenced the relatively weak action of the modified cycloalkaneindoles **IIIa**–**IIIh** on the mentioned binding sites of the NMDA receptor. At the same time, the peripheral Ifenprodil-binding site was more selective towards the prepared compounds structure as compared to the intrachannel site specific for the model ligand MK-801, showing the opportunity of further optimization of the fluorine-containing cycloalkaneindoles (for example, via the introduction of a spacer combining indole and imidazopyridine fragments).

In summary, we developed an original approach towards modification of the cycloalkaneindoles via introduction of fluorine-containing fused heterocycles at the indole nitrogen atom; as an example, the previously unknown 5-[2-(2-trifluoromethylimidazo[1,2-*a*]pyridin-6-yl)]-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]-indoles were prepared. Radioligand study of the products biological activity demonstrated that such compounds class likely contained promising neuroprotective agents.

EXPERIMENTAL

^1H and ^{19}F NMR spectra were recorded using a DPX 200 [200.13 (^1H) and 188.29 (^{19}F) MHz] spectrometer, with $SiMe_4$ as ^1H, internal reference and CF_3COOH as ^{19}F, external reference. Melting points were determined in a glass capillary.

Table 1. Yields, melting points, and elemental analysis data of compounds **IIIb**–**IIIh**

Comp. no.	Yield, %	mp, °C	Found, %			Formula	Calculated, %		
			C	H	N		C	H	N
IIIb	71	179–181	69.29	5.76	10.39	$C_{23}H_{22}F_3N_3$	69.51	5.58	10.57
IIIc	68	122–124	69.35	5.41	10.74	$C_{23}H_{22}F_3N_3$	69.51	5.58	10.57
IIId	65	150–152	64.95	4.59	10.63	$C_{21}H_{17}F_4N_3$	65.11	4.42	10.85
IIIe	72	164–165	66.02	4.91	10.26	$C_{22}H_{19}F_4N_3$	65.83	4.77	10.47
IIIf	75	154–156	65.66	4.89	10.63	$C_{22}H_{19}F_4N_3$	65.83	4.77	10.47
IIIg	77	104–105	65.71	4.89	10.69	$C_{22}H_{19}F_4N_3$	65.83	4.77	10.47
IIIh	70	168–169	65.99	4.56	10.71	$C_{22}H_{19}F_4N_3$	65.83	4.77	10.47

Table 2. ^{1}H and ^{19}F NMR ($CDCl_3$) spectral parameters of compounds **IIIb**–**IIIh**

Comp. no.	δ, ppm (*J*, Hz)	δ_F, ppm (*J*, Hz)
IIIb	1.14 d (3H, $\underline{CH_3}CH$, $^3J_{HH}$ 6.4), 1.40–1.70 m (1H, $CH_3\underline{CH}$), 1.82 s (3H, CH_3C_{Ar}), 1.82–2.08 m (2H, CH_2), 2.14–2.40 m (2H, CH_2), 2.44 s (3H, CH_3C_{Ar}), 2.54 d.t (1H, $\underline{CH_2}CH_2CH$, $^2J_{HH}$ 15.4, $^3J_{HH}$ 5.1), 2.88 d.t (1H, $\underline{CH_2}CH_2CH$, $^2J_{HH}$ 15.4, $^3J_{HH}$ 5.1), 6.58 d (1H, CH_{Ar}, $^3J_{HH}$ 7.0), 6.70 d (1H, CH_{Ar}, $^3J_{HH}$ 8.5), 6.95 d (1H, CH_{Ar}, $^3J_{HH}$ 8.0), 7.26 d.d (1H, CH_{Ar}, $^3J_{HH}$ 9.0, $^3J_{HH}$ 8.0), 7.32 s (1H, CH_{Ar}), 7.64 d (1H, CH_{Ar}, $^3J_{HH}$ 9.0)	15.13, 15.20 (1 : 0.6)
IIIc	1.14 d (3H, $\underline{CH_3}CH$, $^3J_{HH}$ 6.6), 1.40–1.64 m (1H, $CH_3\underline{CH}$), 1.82–2.10 m (2H, CH_2), 2.16–2.60 m (3H, $\underline{CH_2}CH_2CH$ + CH_2), 2.45 s (3H, CH_3C_{Ar}), 2.68 s (3H, CH_3C_{Ar}), 2.87 d.t (1H, $\underline{CH_2}CH_2CH$, $^2J_{HH}$ 15.4, $^3J_{HH}$ 5.1), 6.68 d.d (1H, CH_{Ar}, $^3J_{HH}$ 8.0, $^4J_{HH}$ 3.0), 6.76 d (1H, CH_{Ar}, $^3J_{HH}$ 7.0), 6.93 d (1H, CH_{Ar}, $^3J_{HH}$ 8.0), 7.16 d (1H, CH_{Ar}, $^3J_{HH}$ 7.0), 7.24 d (1H, CH_{Ar}, $^3J_{HH}$ 8.0), 7.34 s (1H, CH_{Ar})	15.61, 15.68 (1 : 0.9)
IIId	1.80–1.96 m (4H, CH_2), 2.17 d.t (1H, $C_{Ar}\underline{CH_2}CH_2$, $^2J_{HH}$ 16.6, $^3J_{HH}$ 5.0), 2.26 s (3H, CH_3), 2.52 d.t (1H, $C_{Ar}\underline{CH_2}CH_2$, $^2J_{HH}$ 16.6, $^3J_{HH}$ 5.0), 2.66–2.86 m (2H, CH_2), 6.72 d.d (1H, CH_{Ar}, $^3J_{HH}$ 8.5, $^3J_{HH}$ 4.4), 6.85 t.d (1H, CH_{Ar}, $^3J_{HH}$ 9.0, $^4J_{HH}$ 2.2), 7.12 s (1H, CH_{Ar}), 7.18–7.30 m (2H, CH_{Ar}), 7.68 d (1H, CH_{Ar}, $^3J_{HH}$ 9.0)	–45.36 t.d ($^3J_{FH}$ 9.0, $^3J_{FH}$ 4.4), 15.36
IIIe	1.14 d (3H, $\underline{CH_3}CH$, *J* 6.6), 1.42–1.68 m (1H, $CH_3\underline{CH}$), 1.78 s (3H, CH_3C_{Ar}), 1.82–2.08 m (2H, CH_2), 2.14–2.42 m (2H, CH_2), 2.54 d.t (1H, $\underline{CH_2}CH_2CH$, $^2J_{HH}$ 15.4, $^3J_{HH}$ 5.1), 2.86 d.t (1H, $\underline{CH_2}CH_2CH$, $^2J_{HH}$ 15.4, $^3J_{HH}$ 5.1), 6.58 d (1H, CH_{Ar}, $^3J_{HH}$ 6.8), 6.72 d.d. d (1H, CH_{Ar}, $^3J_{HH}$ 8.8, $^3J_{HH}$ 4.4, $^4J_{HH}$ 1.7), 6.85 t.d (1H, CH_{Ar}, $^3J_{HH}$ 8.8, $^4J_{HH}$ 2.4), 7.14 d.d (1H, CH_{Ar}, $^3J_{HH}$ 9.3, $^4J_{HH}$ 2.4), 7.28 d.d (1H, CH_{Ar}, $^3J_{HH}$ 9.0, $^3J_{HH}$ 8.8), 7.64 d (1H, CH_{Ar}, $^3J_{HH}$ 9.0)	–45.60 m, 15.06, 15.14 (1 : 0.7)
IIIf	1.14 d (3H, $\underline{CH_3}CH$, $^3J_{HH}$ 6.4), 1.41–1.70 m (1H, $CH_3\underline{CH}$), 1.80–2.07 m (2H, CH_2), 2.14–2.40 m (2H, CH_2), 2.45 d.t (1H, $\underline{CH_2}CH_2CH$, $^2J_{HH}$ 15.0, $^3J_{HH}$ 5.6), 2.71 s (3H, CH_3C_{Ar}), 2.84 d.t (1H, $\underline{CH_2}CH_2CH$, $^2J_{HH}$ 15.0, $^3J_{HH}$ 5.6), 6.65–6.90 m (3H, CH_{Ar}), 7.12–7.28 m (3H, CH_{Ar})	–45.40 m, 15.54, 15.62 (1 : 0.9)
IIIg	1.52–1.76 m (2H, CH_2), 1.77–1.96 m (4H, CH_2), 2.22 c (3H, CH_3), 2.24–2.60 m (2H, CH_2), 2.74–2.90 m (2H, CH_2), 6.64 d.d (1H, CH_{Ar}, $^3J_{HH}$ 8.5, $^3J_{HF}$ 4.3), 6.85 t.d (1H, CH_{Ar}, $^3J_{HF}$ 9.2, $^4J_{HH}$ 2.4), 7.07 s (1H, CH_{Ar}), 7.15–7.30 m (2H, CH_{Ar}), 7.66 d (1H, CH_{Ar}, $^3J_{HF}$ 9.2)	–45.32 t.d ($^3J_{FH}$ 9.2, $^3J_{FH}$ 4.3), 15.30, 15.33 (1 : 0.4)
IIIh	1.50–1.75 m (2H, CH_2), 1.76–2.00 m (4H, CH_2), 2.22–2.66 m (2H, CH_2), 2.72 c (3H, CH_3), 2.74–2.92 m (2H, CH_2), 6.64 d.d (1H, CH_{Ar}, $^3J_{HH}$ 8.8, $^3J_{HF}$ 4.4), 6.75–6.86 m (2H, CH_{Ar}), 7.15–7.26 m (3H, CH_{Ar})	–45.36 t.d ($^3J_{FH}$ 9.3, $^3J_{FH}$ 4.3), 15.52

Parent cycloalkaneindoles **Ia**–**Ie** were prepared as described in [10]; 2-trifluoromethylimidazo[1,2-*a*]-pyridines **IIa**–**IIc** were synthesized according to [11, 12].

6-Methyl-9-(6-methyl-2-trifluoromethylimidazo-[1,2-*a*]pyridin-3-yl)-2,3,4,9-tetrahydro-1*H*-carbazole

Table 3. The action (IC_{50}, μM) of dimebon and compounds **IIIa**–**IIIh** on the binding of labeled ligands [^{3}H]MK-801 and [^{3}H]Ifenprodil with different parts of the NMDA receptor

Compound	[^{3}H]MK-801	[^{3}H]Ifenprodil
Dimebon	91.5±3.7	82.4±4.1
IIIa	≥100	73.89±35.64
IIIb	≥100	>100
IIIc	124.65±1.77	39.51±7.05
IIId	173.73±7.49	>100
IIIe	188.04±9.62	105.4±15.2
IIIf	177.31±8.04	110.4±13.34
IIIg	≥100	>100
IIIh	≥100	>100

(IIIa). A mixture of 1 mmol of tetrahydrocarbazole **Ia**, 1 mmol of 6-methyl-2-trifluoromethyl-3-fluoroimidazo [1,2-*a*]pyridine **IIb**, 1.1 mmol of KOH, and 0.02 g of hydroquinone in 1.5 mL of DMF were heated at 110°C at stirring during 3 h. After the solvent removal, the reaction product was extracted with CH_2Cl_2. Methylene chloride was then removed, and the residue was purified by chromatography on 60 μ silica gel with 1 : 15 methanol–chloroform mixture as eluent. Yield 0.28 g (73%), mp 157–158°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 0.78–1.96 m (4H, CH_2), 2.17 m (1H, $C_{Ar}\underline{CH_2}CH_2$), 2.23 s (3H, CH_3), 2.45 s (3H, CH_3), 2.52 m (1H, $C_{Ar}\underline{CH_2}CH_2$), 2.66–2.88 m (2H, CH_2), 6.70 d (1H, CH_{Ar}, $^3J_{HH}$ 8.5 Hz), 6.95 d (1H, CH_{Ar}, $^3J_{HH}$ 8.3 Hz), 7.15 s (1H, CH_{Ar}), 7.24 d (1H, CH_{Ar}, $^3J_{HH}$ 10.0 Hz), 7.36 s (1H, CH_{Ar}), 7.66 d (1H, CH_{Ar}, $^3J_{HH}$ 10.0 Hz). ^{19}F NMR spectrum ($CDCl_3$): δ_F 15.48 ppm. Found, %: C 68.63; H 5.07; N 11.18. $C_{22}H_{20}F_3N_3$. Calculated, %: C 68.92; H 5.26; N 10.96.

3,6-Dimethyl-9-(5-methyl-2-trifluoromethylimi-dazo[1,2-*a*]pyridin-3-yl)-2,3,4,9-tetrahydro-1*H*-car-

bazole (IIIb), 3,6-dimethyl-9-(8-methyl-2-trifluoromethylimidazo[1,2-*a*]pyridin-3-yl)-2,3,4,9-tetrahydro-1*H*-carbazole (IIIc), 6-fluoro-9-(6-methyl-2-trifluoromethylimidazo[1,2-a]pyridin-3-yl)-2,3,4,9-tetrahydro-1*H*-carbazole (IIId), 3-methyl-6-fluoro-9-(5-methyl-2-trifluoromethylimidazo[1,2-*a*]pyridin-3-yl-2,3,4,9-tetrahydro-1*H*-carbazole (IIIe), 3-methyl-6-fluoro-9-(8-methyl-2-trifluoromethylimidazo[1,2-*a*]pyridin-3-yl)-2,3,4,9-tetrahydro-1*H*-carbazole (IIIf), 5-(6-methyl-2-trifluoromethylimidazo[1,2-*a*]pyridin-3-yl)-2-fluoro-5,6,7,8,9-hexahydrocyclohepta[*b*]indole (IIIg), and 5-(8-methyl-2-trifluoromethylimidazo[1,2-*a*]pyridin-3-yl)-2-fluoro-5,6,7,8,9-hexahydrocyclohepta[*b*]indole (IIIh) were prepared similarly. Yields, melting points, elemental analysis, and spectral data for compounds **IIIb**–**IIIh** are collected in Tables 2 and 3.

ACKNOWLEDGMENTS

This work was financially supported by the Russian Foundation for Basic Research (project no. 14-03-00491-a) and in the frame of the Program of Division of Chemistry and Materials Science of Russian Academy of Sciences "Medicinal chemistry: molecular design of physiologically active compounds and drugs."

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