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Mendeleev Commun., 2005, 15(5), 196–197
Mendeleev Communications

Synthesis and anti-inflammatory activity of dipyrazolopyridines

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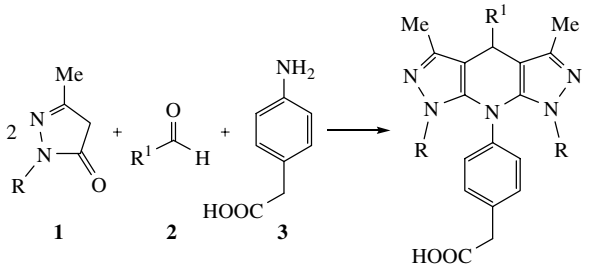
DOI: 10.1070/MC2005v015n05ABEH002129

The synthesis, characterization and anti-inflammatory activity of dipyrazolopyridine derivatives are described.

Pyrazolopyridines exhibit pharmacological activities like anxiolytic[1,2] and anti tumor[3] and tested for their ability to displace flunitrazepam binding from bovine brain membranes.[4] Aryl alkanoic acids are non-steroidal anti-inflammatory drugs, which cover the major NSAIDs[5,6] such as diclofenac sodium, naproxen, ibuprofen *etc*. Interest has focused on the anti-inflammatory activity of a nitrogen-containing nucleus.[7–9]



Scheme 1

Here we report the synthesis of dipyrazolopyridine derivatives **4a–l** (Scheme 1). We attempted to synthesise {4-[1,7-disubstituted-4-(4-substituted aryl)-3,5-dimethyl-4,7-dihydro-1*H*-dipyrazolo[3,4-*b*;4′,3′-*e*]pyridin-8-yl]phenyl}acetic acid derivatives to search for new compounds with potential anti-inflammatory activity. The synthetic pathway was based on the classical Hantzsch synthesis of 1,4-dihydropyridines[10–12] using different aromatic aldehydes **2** with 5-methyl-2-R-2,4-dihydropyrazol-3-one **1** and *p*-aminophenylacetic acid **3** as starting materials (see Scheme 1). Dipyrazolopyridine derivatives **4a–l** could be prepared in good yield. The structures of the new compounds were confirmed by elemental analysis, IR and ^{1}H NMR spectroscopy.†

Table 1 Characterization data and anti-inflammatory activity of compounds **4a–l**.

Entry	R	R^1	Molecular formula (molecular mass)	Activity[a] (%)	Yield (%)
4a	H	Phenyl	$C_{23}H_{21}N_5O_2$ (399.4)	26	65
4b	H	4-Chlorophenyl	$C_{23}H_{20}ClN_5O_2$ (433.9)	22	50
4c	H	4-Methoxyphenyl	$C_{24}H_{23}N_5O_3$ (429.5)	35	60
4d	H	2-Thiophenyl	$C_{21}H_{19}N_5O_2S$ (405.5)	12	50
4e	H	2-Furyl	$C_{21}H_{19}N_5O_3$ (389.4)	18	70
4f	H	3-Nicotinyl	$C_{22}H_{20}N_6O_2$ (400.4)	10	65
4g	Phenyl	Phenyl	$C_{35}H_{29}N_5O_2$ (551.6)	28	60
4h	Phenyl	4-Chlorophenyl	$C_{35}H_{28}ClN_5O_2$ (586.1)	21	65
4i	Phenyl	4-Methoxyphenyl	$C_{36}H_{31}N_5O_3$ (581.7)	31	50
4j	Phenyl	2-Thiophenyl	$C_{33}H_{27}N_5O_2S$ (557.7)	14	60
4k	Phenyl	2-Furyl	$C_{33}H_{27}N_5O_3$ (541.6)	11	65
4l	Phenyl	3-Nicotinyl	$C_{34}H_{28}N_6O_2$ (552.6)	12	65

[a]Activity reference standard: Diclofenac sodium, 47%.

† The purity of compounds was checked by TLC. The IR spectra were recorded on a JASCO spectrophotometer (Japan) using KBr pellets. The ^{1}H and ^{13}C NMR spectra in $CDCl_3$ were measured on a Bruker AC-300F multinuclear FT NMR spectrometer at 300 MHz using TMS as an internal standard. Satisfactory microanalysis data (±0.4% of the calculated values) were obtained for all of the compounds.

*[4-(3,5-Dimethyl-4-phenyl-4,7-dihydro-1*H*-dipyrazolo[3,4-*b*;4′,3′-*e*]-pyridin-8-yl)phenyl]acetic acid* **4a**. To a solution of 5-methyl-2,4-dihydropyrazol-3-one (0.02 mol) and an aldehyde (0.01 mol) in 50 ml of dry ethanol, *p*-aminophenylacetic acid (0.01 mol) was added, and the reaction mixture was refluxed for 8 h. The reaction was monitored by TLC. After completion of the reaction, the reaction mixture was allowed to cool to room temperature. The solid thus obtained was filtered off, washed with cold ethanol, dried and recrystallised; mp 212 °C. ^{1}H NMR ($CDCl_3$) δ: 2.79 (s, 6H, Me), 3.49 (s, 2H, CH_2), 5.34 (s, 1H, CH), 6.2–7.3 (m, 9H, H_{Ar}), 5.9 (s, 2H, NH), 11.1 (br. s, 1H, OH). IR (KBr, ν/cm^{-1}): 3344 (NH), 2600–3200 (br., OH), 1684 (C=O). Found (%): C, 69.14; H, 5.32; N, 17.55. Calc. for $C_{23}H_{21}N_5O_2$ (%): C, 69.16; H, 5.30; N, 17.53. Compounds **4b–l** were obtained similarly to **4a**.

*{4-[4-(4-Chlorophenyl)-3,5-dimethyl-4,7-dihydro-1*H*-dipyrazolo[3,4-*b*;4′,3′-*e*]pyridin-8-yl]phenyl}acetic acid* **4b**: mp 191 °C. ^{1}H NMR ($CDCl_3$) δ: 2.82 (s, 6H, Me), 3.3 (s, 2H, CH_2), 5.3 (s, 1H, CH), 6.2–7.5 (m, 8H, H_{Ar}), 5.8 (s, 2H, NH), 11.0 (br. s, 1H, OH). IR (KBr, ν/cm^{-1}): 3350 (NH), 2600–3200 (br., OH), 1690 (C=O). Found (%): C, 63.69 ; H, 4.67; N, 16.12. Calc. for $C_{23}H_{20}ClN_5O_2$ (%): C, 63.67; H, 4.65; N, 16.14.

*{4-[4-(4-Methoxyphenyl)-3,5-dimethyl-4,7-dihydro-1*H*-dipyrazolo-[3,4-*b*;4′,3′-*e*]pyridin-8-yl]phenyl}acetic acid* **4c**: mp 237 °C. ^{1}H NMR ($CDCl_3$) δ: 2.7 (s, 6H, Me), 3.4 (s, 2H, CH_2), 3.7 (s, 3H, OMe), 5.4 (s, 1H, CH), 6.1–7.7 (m, 8H, H_{Ar}), 5.9 (s, 2H, NH), 11.2 (br. s, 1H, OH). IR (KBr, ν/cm^{-1}): 3375 (NH), 2650–3200 (br., OH), 1680 (C=O). Found (%): C, 67.14; H, 5.44; N, 16.35. Calc. for $C_{24}H_{23}N_5O_3$ (%): C, 67.12; H, 5.40; N, 16.31.

*[4-(3,5-Dimethyl-4-thiophen-2-yl-4,7-dihydro-1*H*-dipyrazolo[3,4-*b*;4′,3′-*e*]pyridin-8-yl)phenyl]acetic acid* **4d**: mp 258 °C. ^{1}H NMR ($CDCl_3$) δ: 2.8 (s, 6H, Me), 3.3 (s, 2H, CH_2), 5.34 (s, 1H, CH), 6.2–7.5 (m, 7H, H_{Ar}), 6.1 (s, 2H, NH), 11.2 (br. s, 1H, OH). IR (KBr, ν/cm^{-1}): 3340 (NH), 2600–3250 (br., OH), 1695 (C=O). Found (%): C, 62.20; H, 4.71; N, 17.29; S, 7.93. Calc. for $C_{21}H_{19}N_5O_2S$ (%): C, 62.21; H, 4.72; N, 17.27; S, 7.91.

*[4-(4-Furan-2-yl-3,5-dimethyl-4,7-dihydro-1*H*-dipyrazolo[3,4-*b*;4′,3′-*e*]-pyridin-8-yl)phenyl]acetic acid* **4e**: mp 216 °C. ^{1}H NMR ($CDCl_3$) δ: 2.7 (s, 6H, Me), 3.4 (s, 2H, CH_2), 5.3 (s, 1H, CH), 6.4–7.3 (m, 7H, H_{Ar}), 5.9 (s, 2H, NH), 11.1 (br. s, 1H, OH). IR (KBr, ν/cm^{-1}): 3360 (NH), 2600–3200 (br., OH), 1680 (C=O). Found (%): C, 64.80; H, 4.89; N, 17.96. Calc. for $C_{21}H_{19}N_5O_3$ (%): C, 64.77; H, 4.92; N, 17.98.

The compounds were tested for anti-inflammatory activity according to the published method.[13] The percentage reduction in inflammation (*i.e.*, reduction in the left hand paw edema volume of the animals)‡ after 3 h of administration of carangeenan was recorded, and the test compound was compared with that of the animals administered with carangeenan using the reference standard diclofenac sodium. The anti-inflammatory activities of all the compounds are given in Table 1.

All the compounds showed a tendency to cause a fall in edema and showed anti-inflammatory activity. The anti-inflammatory activity data shows that the presence of a *p*-methoxyphenyl group at C-4 plays an important role in the activity of compounds **4c** and **4i**, *i.e.*, it enhances the anti-inflammatory activity. The presence of a phenyl group at C-4 also shows good anti-inflammatory activity, but the phenyl group at the nitrogen atom of pyrazole cannot enhance the anti-inflammatory activity. *p*-Chlorophenyl at C-4 shows a moderate activity of compounds **4b** and **4h**. The presence of a heterocyclic moiety at C-4 reduces the anti-inflammatory activity.

*[4-(3,5-Dimethyl-4-pyridin-3-yl-4,7-dihydro-1*H*-dipyrazolo[3,4-*b*;4',3'-*e*]pyridin-8-yl)phenyl]acetic acid* **4f**: mp 202 °C. ^{1}H NMR ($CDCl_3$) δ: 2.86 (s, 6H, Me), 3.4 (s, 2H, CH_2), 5.34 (s, 1H, CH), 6.2–7.9 (m, 8H, H_{Ar}), 6.0 (s, 2H, NH), 11.1(br. s, 1H, OH). IR (KBr, ν/cm^{-1}): 3350 (NH), 2600–3200 (br., OH), 1685 (C=O). Found (%): C, 65.96; H, 5.05; N, 20.95. Calc. for $C_{22}H_{20}N_6O_2$ (%): C, 65.99; H, 5. 03; N, 20.99.

*[4-(3,5-Dimethyl-1,4,7-triphenyl-4,7-dihydro-1*H*-dipyrazolo[3,4-*b*;4',3'-*e*]pyridin-8-yl)phenyl]acetic acid* **4g**: mp 219 °C. ^{1}H NMR ($CDCl_3$) δ: 2.74 (s, 6H, Me), 3.4 (s, 2H, CH_2), 5.34 (s, 1H, CH), 6.1–7.3 (m, 19H, H_{Ar}), 11.0 (br. s, 1H, OH). IR (KBr, ν/cm^{-1}): 2650–3250 (br., OH), 1670 (C=O). Found (%): C, 76.22; H, 5.29; N, 12.68. Calc. for $C_{35}H_{29}N_5O_2$ (%): C, 76.20; H, 5.30; N, 12.70.

*{4-[4-(4-Chlorophenyl)-3,5-dimethyl-1,7-diphenyl-4,7-dihydro-1*H*-dipyrazolo[3,4-*b*;4',3'-*e*]pyridin-8-yl]phenyl}acetic acid* **4h**: mp 245 °C. ^{1}H NMR ($CDCl_3$) δ: 2.82 (s, 6H, Me), 3.4 (s, 2H, CH_2), 5.4 (s, 1H, CH), 6.2–7.3 (m, 18H, H_{Ar}), 11.3 (br. s, 1H, OH). IR (KBr, ν/cm^{-1}): 2600–3200 (br., OH), 1690 (C=O). Found (%): C, 71.74; H, 4.85; N, 11.96. Calc. for $C_{35}H_{28}ClN_5O_2$ (%): C, 71.30; H, 4.82; N, 11.95.

*{4-[4-(4-Methoxyphenyl)-3,5-dimethyl-1,7-diphenyl-4,7-dihydro-1*H*-dipyrazolo[3,4-*b*;4',3'-*e*]pyridin-8-yl]phenyl}acetic acid* **4i**: mp 209 °C. ^{1}H NMR ($CDCl_3$) δ: 2.79 (s, 6H, Me), 3.44 (s, 2H, CH_2), 3.73 (s, 3H, OMe), 5.34 (s, 1H, CH), 6.2–7.7 (m, 18H, H_{Ar}), 11.1 (br. s, 1H, OH). IR (KBr, ν/cm^{-1}): 2600–3200 (br., OH), 1700 (C=O). Found (%): C, 74.36; H, 5.34; N, 12.01. Calc. for $C_{36}H_{31}N_5O_3$ (%): C, 74.34; H, 5.37; N, 12.04.

*[4-(3,5-Dimethyl-1,7-diphenyl-4-thiophen-2-yl-4,7-dihydro-1*H*-dipyrazolo[3,4-*b*;4',3'-*e*]pyridin-8-yl)phenyl]acetic acid* **4j**: mp 227 °C. ^{1}H NMR ($CDCl_3$) δ: 2.75 (s, 6H, Me), 3.4 (s, 2H, CH_2), 5.34 (s, 1H, CH), 6.2–7.3 (m, 17H, H_{Ar}), 11.1 (br. s, 1H, OH). IR (KBr, ν/cm^{-1}): 2600–3200 (br., OH), 1678 (C=O). Found (%): C, 71.04 ; H, 4.89; N, 12.59; S, 5.77. Calc. for $C_{33}H_{27}N_5O_2S$ (%): C, 71.07; H, 4.88; N, 12.56; S, 5.75.

*[4-(4-Furan-2-yl-3,5-dimethyl-1,7-diphenyl-4,7-dihydro-1*H*-dipyrazolo-[3,4-*b*;4',3'-*e*]pyridin-8-yl)phenyl]acetic acid* **4k**: mp 199 °C. ^{1}H NMR ($CDCl_3$) δ: 2.9 (s, 6H, Me), 3.4 (s, 2H, CH_2), 5.34 (s, 1H, CH), 6.3–7.6 (m, 17H, H_{Ar}), 11.1 (br. s, 1H, OH). IR (KBr, ν/cm^{-1}): 2650–3200 (br., OH), 1680 (C=O). Found (%): C, 73.16; H, 5.02; N, 12.95. Calc. for $C_{33}H_{27}N_5O_3$ (%): C, 73.18; H, 5.02; N, 12.93.

*[4-(3,5-Dimethyl-1,7-diphenyl-4-pyridin-3-yl-4,7-dihydro-1*H*-dipyrazolo[3,4-*b*;4',3'-*e*]pyridin-8-yl)phenyl]acetic acid* **4l**: mp 240 °C. ^{1}H NMR ($CDCl_3$) δ: 2.79 (s, 6H, Me), 3.4 (s, 2H, CH_2), 5.34 (s, 1H, CH), 6.3–7.3 (m, 18H, H_{Ar}), 11.1 (br. s, 1H, OH). Found (%): C, 71.04; H, 4.89; N, 12.59. Calc. for $C_{34}H_{28}N_6O_2$ (%): C, 71.07; H, 4.88; N, 12.56.

‡ *Carangeenan induced rat paw edema test*. Albino rats (150–200 g) were divided into groups containing six animals each. The animals were fasted for 12 h before experiments and only water was allowed. While the first group was a control one and received a vehicle [Tween 80 in propylene glycol (10 vol%), 0.5 ml per rat], the second group received diclofenac sodium (10 mg kg^{-1} body mass). All the remaining groups received the test compounds at the same dose orally. All the suspensions for oral dose were prepared in the above vehicle and administered in a constant volume of 0.5 ml per rat. One hour after the administration of the test compound and diclofenac sodium, 0.1 ml of a 1% w/v suspension of carangeenan was injected into the subplanatar of left paw of control and test animals. Immediately, the paw volume was measured using a plethismometer (initial paw volume), thereafter the paw volume was measured every half an hour for 3 h. The difference between initial and subsequent readings gave the edema volume for the corresponding time. Percentage inhibition was calculated (Table 1).

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Received: 21st January 2005; Com. 05/2452