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# *N*-Substituted 3-(arylamino)-4,5-dihydro-2*H*-benz[*g*]indazol-2-yl acetamides with anti-inflammatory and analgesic activities

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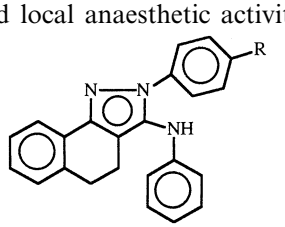
**Abstract**

A series of substituted 3-(arylamino)-4,5-dihydro-2*H*-benz[*g*]indazol-2-yl acetamides was synthesized and tested in comparison with former analogues. The title compounds showed only weak antiarrhythmic properties but good anti-inflammatory and antinociceptive activity, particularly evident in the morpholino derivative. © 2000 Published by Elsevier Science S.A. All rights reserved.

*Keywords:* *N*-Substituted 4,5-dihydro-2*H*-benz[*g*]indazol-2-yl acetamides; Anti-inflammatory agents; Analgesic agents

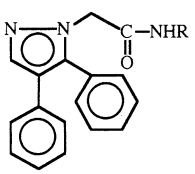
## 1. Introduction

Our previous work dealing with the biological activity of simple and complex pyrazole derivatives enabled us to study a series of 2-aryl-3-phenylamino-4,5-dihydro-2*H*-benz[*g*]indazoles **1** that showed interesting antiarrhythmic and local anaesthetic activities [1].



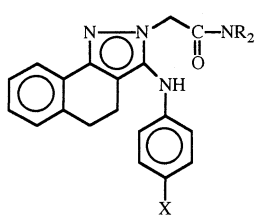

**1**

On the other hand, diphenyl-substituted pyrazolyl acetamides **2** were early prepared and tested as antiarrhythmic agents by Bailey [2].




**2**

It was with these observations in mind that we have been engaged in the preparation of other analogues of **1** bearing in position 2 of the benzindazole ring a substituted acetamido moiety instead of an aryl group:




In our compounds the rigid tetralone moiety takes the place of the two phenyl rings present in compounds **2**, thus maintaining comparable lipophilic features.

We also tried the effect of the *p*-substitution with halogen atoms in the phenylamino group in order to verify their influence on the pharmacological profile.

## 2. Chemistry

The synthetic approach started from 1-tetralone **3** which was reacted with the proper *p*-substituted phenylisothiocyanates to give the corresponding oxocarbothioamides **4** in good yield.

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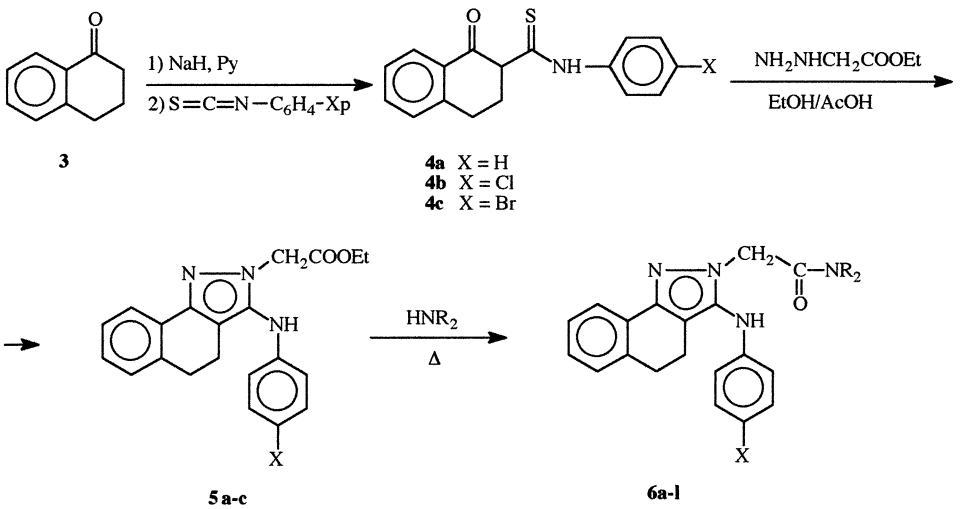


| Comp. | X | $NR_2$ | Comp. | X | $NR_2$ |
|---|---|---|---|---|---|
| **6a** | H | $NHCH(CH_3)_2$ | **6f** | Cl | $NH(CH_2)_2OCH_2CH_3$ |
| **6b** | H | $NH(CH_2)_2OCH_2CH_3$ | **6g** | Cl | $NHCH_2C_6H_5$ |
| **6c** | H | $NHCH_2C_6H_5$ | **6h** | Cl | morpholino |
| **6d** | H | morpholino | **6i** | Br | $NH(CH_2)_2OCH_2CH_3$ |
| **6e** | Cl | $NHCH(CH_3)_2$ | **6l** | Br | morpholino |

Reaction of **4** with ethyl hydrazinoacetate gave the ethyl esters **5**, which in turn, by heating with the relevant amines, led to the desired substituted amides **6** in good yield.

The direct cyclization of **4** to **5**, without isolation of hydrazone intermediates, was achieved as in the former series [1] by heating the reaction mixture with a catalytic amount of acetic acid and elimination of hydrogen sulfide.

## 3. Pharmacology

Compounds **6a**–**l** were submitted to a preliminary screening for anti-inflammatory, analgesic, antiarrhythmic and local anaesthetic activities.

## 4. Experimental

### 4.1. Chemistry

Melting points were determined with a Büchi 530 apparatus. IR spectra were measured in KBr with a Perkin–Elmer 398 spectrophotometer. $^1H$ NMR spectra were recorded in $CDCl_3$ solution on a Hitachi Perkin–Elmer R-600 (60 MHz) instrument, chemical shifts are reported as $\delta$ (ppm) relative to TMS as internal standard; $J$ in Hz. Analyses for C, H, N were within $\pm 0.3\%$ of the theoretical values.

#### 4.1.1. General procedure for N-aryl-3,4-dihydro-1(2H)-oxonaphtalene-2-carbothioamides (4a–c)

To a cold solution of 1-tetralone (2.92 g, 20 mmol) in dry dimethylformamide (DMF, 15 ml), a 60% sodium hydride dispersion in mineral oil (0.80 g, 20 mmol) was added and the resulting mixture was stirred at room temperature (r.t.) until the hydrogen evolution subsided. The proper arylisothiocyanate (21 mmol) was then added and the mixture was stirred at r.t. for 4 h, poured cautiously into cold water (100 ml) and extracted with petroleum ether (b.p. 40–70°C). The aqueous solution was cooled and acidified with 1 M HCl (pH 4–5).

The solid precipitate was settled, filtered, washed with water and finally crystallized from absolute ethanol.

**4a**: yield 80%; ivory–white crystals, m.p. 137–138°C, lit. [1].

**4b**: yield 92%; ivory–white crystals, m.p. 160–162°C. IR ($CHCl_3$): 3300 and 1664 (NH and CO) $cm^{-1}$; $^1H$ NMR: $\delta$ 2.2–3.3 (m, 4H, $2CH_2$), 3.9–4.3 (m, 1H, CH), 7.2–7.7 and 7.8–8.2 (2m, 8H Ar), 11.30 (s, 1H, NH, disappears with $D_2O$). *Anal.* $C_{17}H_{14}ClNOS$ (C, H, N).

**4c**: yield 70%; ivory–white crystals, m.p. 144–145°C. IR ($CHCl_3$): 3140 and 1672 (NH and CO) $cm^{-1}$; $^1H$

Table 1
Yields, physical and spectroscopic data of compounds **6a–l**

| Comp. | M.p. (°C) | Yield (%) | IR ($CHCl_3$) ($cm^{-1}$) | $^1H$ NMR $\delta$ (ppm) | Formula |
|---|---|---|---|---|---|
| **6a** | 194–195 | 78 | 3290 (NH), 1665 (CO) | 1.02 (d, $J = 7$, 6H, $2CH_3$), 2.30–2.70 and 2.70–3.11 (2m, 4H, $2CH_2$), 3.75–4.30 (sept, $J = 7$, 1H, CH), 4.85 (s, 2H, $CH_2CO$), 6.48 (s, 1H, NH Ar, disappears with $D_2O$), 6.70–7.45 and 7.70–8.00 (2m, 10H, 9H Ar + NH, 1H disappears with $D_2O$) | $C_{22}H_{24}N_4O$ |
| **6b** | 127–129 | 90 | 3380, 1670 | 1.09 (t, $J = 7$, 3H, $CH_3$), 2.30–2.70 and 2.72–3.11 (2m, 4H, $2CH_2$), 3.20–3.80 (m, 6H, $2CH_2O + CH_2N$), 4.80 (s, 2H, $CH_2CO$), 6.12 (s, 1H, NH Ar, disappears with $D_2O$), 6.55–7.55 and 7.70–8.08 (2m, 10H, 9H Ar + NH, 1H disappears with $D_2O$) | $C_{23}H_{26}N_4O_2$ |
| **6c** | 168–170 | 76 | 3300, 1665 | 2.35–2.70 and 2.77–3.12 (2m, 4H, $2CH_2$), 4.30–4.55 (m, 2H, $CH_2N$), 4.86 (s, 2H, $CH_2CO$), 6.19 (s, 1H, NH Ar, disappears with $D_2O$), 6.55–7.51 and 7.70–8.00 (2m, 15H, 14H Ar + NH, 1H disappears with $D_2O$) | $C_{26}H_{24}N_4O$ |
| **6d** | 213–214 | 72 | 3380, 1660 | 2.30–2.70 and 2.75–3.10 (2m, 4H, $2CH_2$), 3.65 (near s, 8H morph), 4.98 (s, 2H, $CH_2CO$), 6.16 (s, 1H, NH, disappears with $D_2O$), 6.60–7.45 and 7.69–8.05 (2m, 9H Ar) | $C_{23}H_{24}N_4O_2$ |
| **6e** | 208–210 | 77 | 3275, 1663 | 1.02 (d, $J = 7$, 6H, $2CH_3$), 2.30–2.70 and 2.77–3.11 (2m, 4H, $2CH_2$), 3.70–4.26 (sept, $J = 7$, 1H, CH), 4.87 (s, 2H, $CH_2CO$), 6.55–7.50 and 7.70–8.00 (2m, 10H, 8H Ar + 2NH, 2H disappear with $D_2O$) | $C_{22}H_{23}ClN_4O$ |
| **6f** | 169–170 | 70 | 3300, 1672 | 1.10 (t, $J = 7$, 3H, $CH_3$), 2.25–2.69 and 2.71–3.10 (2m, 4H, $2CH_2$), 3.20–3.73 (m, 6H, $2CH_2O + CH_2N$), 4.80 (s, 2H, $CH_2CO$), 6.41 (s, 1H, NH disappears with $D_2O$), 6.50–7.47 and 7.68–8.02 (2m, 9H, 8H Ar + NH, 1H disappears with $D_2O$) | $C_{23}H_{25}ClN_4O_2$ |
| **6g** | 206–207 | 90 | 3210, 1667 | 2.20–2.60 and 2.70–3.05 (2m, 4H, $2CH_2$), 4.20–4.49 (m, 2H, $CH_2N$), 4.80 (s, 2H, $CH_2CO$), 6.60–7.45 and 7.60–7.90 (2m, 13H Ar), 8.00 (s, 1H, NH disappears with $D_2O$), 8.38–8.70 (br s, 1H, NH, disappears with $D_2O$) [a] | $C_{26}H_{23}ClN_4O$ |
| **6h** | 199–200 | 77 | 3360, 1667 | 2.30–2.70 and 2.77–3.11 (2m, 4H, $2CH_2$), 3.68 (near s, 8H morph), 4.96 (s, 2H, $CH_2CO$), 6.28 (s, 1H, NH disappears with $D_2O$), 6.60–7.50 and 7.70–8.02 (2m, 8H Ar) | $C_{23}H_{23}ClN_4O_2$ |
| **6I** | 178–180 | 71 | 3340, 1663 | 1.10 (t, $J = 7$, 3H, $CH_3$), 2.25–2.65 and 2.70–3.10 (2m, 4H, $2CH_2$), 3.20–3.71 (m, 6H, $2CH_2O + CH_2N$), 4.77 (s, 2H, $CH_2CO$), 6.21 (s, 1H, NH, disappears with $D_2O$), 6.40–7.60 and 7.67–8.00 (2m, 9H, 8H Ar + NH, 1H disappears with $D_2O$) | $C_{23}H_{25}BrN_4O_2$ |
| **6l** | 190 (dec.) | 65 | 3370, 1658 | 2.30–2.68 and 2.70–3.10 (2m, 4H, $2CH_2$), 3.65 (near s, 8H morph), 4.96 (s, 2H, $CH_2N$), 6.31 (s, 1H, NH disappears with $D_2O$), 6.50–7.52 and 7.60–8.02 (2m, 8H Ar) | $C_{23}H_{23}BrN_4O_2$ |

[a] In DMSO-$d_6$.

NMR: $\delta$ 2.6–3.4 (m, 4H, $2CH_2$), 3.6–4.0 (m, 1H, CH), 7.2–8.3 (m, 8H Ar), 10.82 (br s, 1H, NH, disappears with $D_2O$). *Anal.* $C_{17}H_{14}BrNOS$ (C, H, N).

#### 4.1.2. General procedure for ethyl 3-(arylamino)-4,5-dihydro-2H-benz[g]indazol-2-yl acetates (5a–c)

To a solution of sodium ethoxide prepared from sodium (0.46 g, 20 mmol) in absolute ethanol (25 ml), ethyl hydrazino acetate hydrochloride (3.4 g, 22 mmol) was added and the resulting suspension was stirred at r.t. for 5 min. Then the relevant β-oxothioamide and a small quantity (5 drops) of glacial acetic acid were added and the mixture refluxed for 12 h. The solvent was removed under reduced pressure and the residue treated with water (100 ml), filtered and crystallized from absolute ethanol.

**5a**: yield 58%; light yellow crystals, m.p. 149–150°C. IR ($CHCl_3$): 3395 and 1740 (NH and CO) $cm^{-1}$. $^1H$ NMR: $\delta$ 1.23 (t, $J = 7.2$, 3H, $CH_3$), 2.3–2.7 and 2.7–3.1 (2m, 4H, $2CH_2$), 4.23 (q, $J = 7.2$, 2H, $CH_2O$), 4.89 (s, 2H, $CH_2$–N), 5.56 (s, 1H, NH disappears with $D_2O$), 6.6–7.5 and 7.7–8.1 (2m, 9H Ar). *Anal.* $C_{21}H_{21}N_3O_2$ (C, H, N).

**5b**: yield 58%; light yellow crystals, m.p. 159–160°C. IR ($CHCl_3$): 3380 and 1739 (NH and CO) $cm^{-1}$. $^1H$ NMR: $\delta$ 1.25 (t, $J = 7.2$, 3H, $CH_3$), 2.3–2.7 and 2.7–3.1 (2m, 4H, $2CH_2$), 4.22 (q, $J = 7.2$, 2H, $CH_2O$), 4.87 (s, 2H, $CH_2N$), 5.63 (s, 1H, NH, disappears with $D_2O$), 6.5–7.4 and 7.7–8.10 (2m, 8H Ar), *Anal.* $C_{21}H_{20}ClN_3O_2$ (C, H, N).

**5c**: yield 60%; light yellow crystals, m.p. 143–144°C. IR ($CHCl_3$): 3385 and 1738 (NH and CO) $cm^{-1}$. $^1H$ NMR: $\delta$ 1.25 (t, $J = 7.2$, 3H, $CH_3$), 2.3–2.7 and 2.7–3.1 (2m, 4H, $2CH_2$), 4.23 (q, $J = 7.2$, 2H, $CH_2O$), 4.89 (s, 2H, $CH_2N$), 5.59 (s, 1H, NH, disappears with $D_2O$), 6.5–6.9 and 7.7–8.1 (2m, 8H Ar). *Anal.* $C_{21}H_{20}BrN_3O_2$ (C, H, N).

#### 4.1.3. General procedure for N-substituted 3-(arylamino)-4,5-dihydro-2H-benz[g]indazol-2-yl acetamides (6a–l)

Ethyl acetates **5a**–**c** (10 mmol) and an excess (5 ml) of the suitable amine were heated at reflux (in the case of isopropylamine) or at 100°C (in the case of other amines) for 4 h. Excess amine was removed under reduced pressure and the residue was dissolved in chloroform (20 ml) and washed with 1 M HCl (10 ml) and water. The organic phase was dried (anhyd. $MgSO_4$), filtered and evaporated under reduced pressure to give a crude solid that was crystallized from absolute ethanol. Yields, melting points and spectral data of **6a**–**l** are reported in Table 1.

### 4.2. Pharmacology

Anti-inflammatory activity was evaluated by carrageenan-induced paw edema in rats [3]; analgesic activity was evaluated by the acetic acid writhing test in mice [4]; antiarrhythmic activity was evaluated as protection index against ecgraphic effects from aconitine in rats [5] and local anaesthetic activity was evaluated as infiltration anesthesia in rats [6].

## 5. Result and discussion

As a general consideration, compounds **6a**–**l** poorly confirm the features of previous congeners **1** showing only weak antiarrhythmic (Table 2) and no local anaesthetic activity.

On the other hand a good anti-inflammatory activity turns out to be present in almost all **6a**–**l** (Table 3) with a maximum for **6l** having an $ED_{50}$ of 15.91 (12.61–20.01) and 19.62 (14.91–25.82) mg/kg per o.s. after 3 and 4 h, respectively.

Table 2
Activity against ventricular fibrillation caused by aconitine in albino rats [a]

| Comp. | Dose (mg/kg p.o.) | Appearance time of extrasystoles (s ± SEM) | Death time (s ± SEM) |
|---|---|---|---|
| Control (aconitine HCl) | [b] | 180 ± 16.1 | 596 ± 19.3 |
| Quinidine | 25 | 385 ± 20.2 [c] | 1007 ± 15.6 [c] |
| **6a** | 50 | 194 ± 15.7 | 621 ± 16.3 |
| **6b** | 50 | 187 ± 20.1 | 583 ± 15.8 |
| **6c** | 50 | 232 ± 18.6 | 712 ± 22.3 |
| **6d** | 50 | 198 ± 15.7 | 671 ± 18.7 |
| **6e** | 50 | 224 ± 17.5 | 607 ± 19.5 |
| **6f** | 50 | 307 ± 14.5 | 785 ± 23.4 |
| **6g** | 50 | 196 ± 20.4 | 691 ± 16.3 |
| **6h** | 50 | 205 ± 19.7 | 677 ± 19.1 |
| **6i** | 50 | 198 ± 19.7 | 647 ± 18.5 |
| **6l** | 50 | 263 ± 22.3 | 694 ± 17.1 |

[a] Five animals (200–250 g)/group.
[b] 15 μg/kg i.v. until death.
[c] Statistically significant value calculated in comparison with the test performed with aconitine only ($P < 0.01$).

Table 3
Anti-inflammatory activity by carrageenan-induced rat paw edema test [a] of compounds **6a–l**

| Comp. | Dose (mg/kg) | Edema inhibition (%) relative to control at the following times (h) after treatment | | | |
|---|---|---|---|---|---|
| | | 1 | 2 | 3 | 4 |
| Indomethacin | 5 | −45 | −55 | −63 | −68 |
| **6a** | 50 | −32 | −26 | −39 | −35 |
| **6b** | 50 | −38 | −50 | −45 | −53 |
| **6c** | 50 | −45 | −39 | −50 | −57 |
| **6d** | 50 | −58 | −66 | −56 | −63 |
| **6e** | 50 | −39 | −34 | −45 | −42 |
| **6f** | 50 | −58 | −47 | −41 | −50 |
| **6g** | 50 | −61 | −50 | −58 | −53 |
| **6h** | 50 | −55 | −44 | −39 | −35 |
| **6i** | 50 | −64 | −58 | −52 | −59 |
| **6l** | 12.5 | −58 | −47 | −43 | −39 |
| | 25 | −71 | −63 | −63 | −57 |
| | 50 | −68 | −73 | −78 | −70 |

[a] Each compound was tested on a group of five albino rats (180–250 g). Compounds were given by gastric probe 30 min before carrageenan (0.1 ml of 1% solution).

Table 4
Acetic acid writhing test: analgesic activity

| Comp. | Dose (mg/kg) | Mean number of writhes in 25 min period after treatment ± SEM | % Decrease relative to controls |
|---|---|---|---|
| Control | Acetic acid 0.5% | 46.1 ± 5.7 | |
| Indomethacin | 5 | 23.6 ± 3.9 | −53 |
| **6a** | 50 | 25.3 ± 5.2 | −45 |
| **6b** | 50 | 28.6 ± 4.6 | −38 |
| **6c** | 50 | 31.5 ± 3.4 | −32 |
| **6d** | 50 | 29.5 ± 3.9 | −36 |
| **6e** | 50 | 29.2 ± 3.8 | −37 |
| **6f** | 50 | 24.1 ± 5.1 | −48 |
| **6g** | 50 | 27.2 ± 6.8 | −41 |
| **6h** | 12.5 | 29.5 ± 4.8 | −36 |
| | 25 | 26.3 ± 6.9 | −43 |
| | 50 | 22.8 ± 7.2 | −51 |
| **6i** | 50 | 26.8 ± 7.1 | −42 |
| **6l** | 50 | 24.1 ± 6.2 | −48 |

Furthemore a fairly remarkable antinociceptive effect was evidenced for all compounds **6a–l** (Table 4) at a dose of 50 mg/kg, the most potent being **6h** with an $ED_{50}$ of 47.91 (26.42–86.87) mg/kg per o.s., showing the same antinociceptive property of indomethacin (5 mg/kg) at a dose of 50 mg/kg per o.s.

As a matter of fact the change of the aryl moiety in position 2 of the benzindazole nucleus with a substituted acetamide function does not confirm the antiarrhythmic action proved by derivatives **1** and typical of pyrazole–acetamides **2**.

It is worthwhile noting that compound **6l** elicited the maximum of anti-inflammatory activity and outstanding analgesic effect, whereas the maximum of analgesic activity was achieved by **6h**. Both these derivatives carried out in position 3 a phenyl ring *p*-substituted with a halogen atom (Br and Cl, respectively) and had a morpholino–acetamide chain in position 2.

The morpholino–acetamido analogue **6d**, without a *p*-substitution in the phenyl ring, showed only a considerable anti-inflammatory action.

Evidently the morpholino moiety is the best substituent among the tested *N*-substituted acetamides, whereas the presence of a lipophilic, electron-withdrawing halogen group enhances activity level.

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