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New 2 *H*-benz[*g*]indazoles of anticipated molluscicidal activity

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A facile synthetic approach towards the synthesis of 2-substituted carbamoyl (or thiocarbamoyl)-3-aryl-3,3a,4,5-tetrahydro-2 *H*-benz[*g*]indazoles **3a**–**r** and their 2-acylating derivatives **4**–**6** was reported via the reaction of 2-unsubstituted-2 *H*-benz[*g*]indazoles **2** with isocyanates or their thio analogues, acid anhydrides and aliphatic or aromatic carboxylic acids. The molluscicidal activity of the products was screened.

1. Introduction

Many benzindazoles have been reported to exhibit antifungal [1, 2], herbicidal [3] and antiinflammatory [4, 5] activities. Others act on the nervous system agents [6] or as cholesterol biosynthesis inhibitors [7]. In addition, many 2-substituted carbamoyl benzindazoles were reported to possess remarkable arthropodicidal [8–11] and insecticidal [12] activity. In the light of all the previous reports it was intended in the present work to investigate the synthesis of 2-carbamoyl-2 *H*-benz[*g*]indazoles or their thio-analogues as well as their 2-acyl derivatives in an attempt to find a biologically active compound that may be useful as a molluscicidal agent against the intermediate host of *Schistosoma mansoni*.

2. Investigations, results and discussion

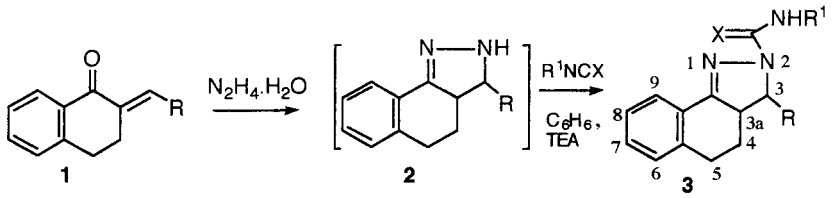
2.1. Synthesis of the compounds

Reaction of 2-arylmethylidene-3,4-dihydro-1(2 *H*)-naphthalenones **1a**–**d** with hydrazine hydrate in boiling ethanol afforded colourless products which gradually darkened at room temperature and eventually decomposed to oily material within few hours in contact with air. This behaviour is not unusual and is in accordance with the well known characters of 1-unsubstituted-2-pyrazoline ring derivatives [13, 14]. So, the isolated 2-unsubstituted-2 *H*-benz[*g*]-indazoles **2** were directly used in the next reaction without any further purification to avoid decomposition.

Electrophilic addition of a variety of aryl, alkyl isocyanates or their thio analogues to the formed 2-unsubstituted-3-aryl-3,3a,4,5-tetrahydro-2 *H*-benz[*g*]indazoles **2a**–**d** afforded exclusively the corresponding carbamoyl or thiocarbamoyl derivatives **3a**–**p**. The structure of which was established through IR, ^{1}H NMR, ^{13}C NMR as well as elemental analyses data. The ^{1}H NMR spectra of 2-methylthiocarbamoyl derivatives **3j**–**l** reveal the presence of the methyl protons as doublet signals ($\delta = 3.17–3.18$, $J = 4.8–5$ Hz). This is due to the mutual coupling between the methyl protons and the vicinal NH thiocarbamoyl proton.

Upon addition of D_2O, the doublet methyl protons signal changed to a sharp singlet. ^{13}C NMR spectrum of **3j** as a representitive example added good support for the pro-

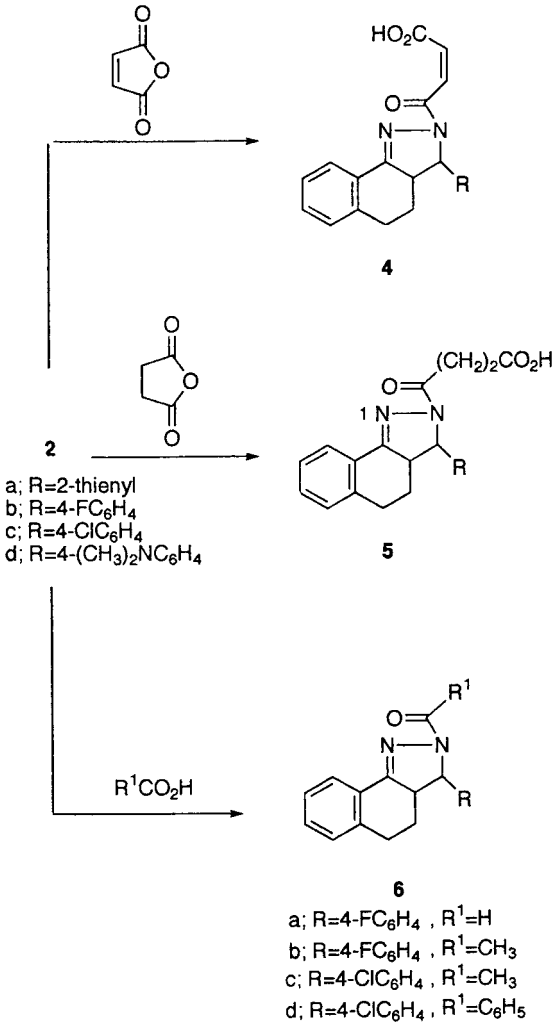
Scheme 1



a; R=2-thienyl
b; R=4-FC_6H_4
c; R=4-ClC_6H_4
d; R=4-$(CH_3)_2NC_6H_4$

	R	R^1	X
a	2-thienyl	3,4-$Cl_2C_6H_3$	O
b	4-FC_6H_4	3,4-$Cl_2C_6H_3$	O
c	4-ClC_6H_4	3,4-$Cl_2C_6H_3$	O
d	4-$(CH_3)_2NC_6H_4$	3,4-$Cl_2C_6H_3$	O
e	2-thienyl	4-$CH_3OC_6H_4$	O
f	4-FC_6H_4	4-$CH_3OC_6H_4$	O
g	4-ClC_6H_4	4-$CH_3OC_6H_4$	O
h	2-thienyl	C_6H_5	S
i	4-FC_6H_4	C_6H_5	S
j	2-thienyl	CH_3	S
k	4-FC_6H_4	CH_3	S
l	4-ClC_6H_4	CH_3	S
m	4-$(CH_3)_2NC_6H_4$	CH_3	S
n	2-thienyl	C_2H_5	O
o	2-thienyl	C_2H_5	S
p	4-FC_6H_4	C_2H_5	S
q	2-thienyl	β-glucopyranosyl-2,3,4,6-tetraacetate	S
r	4-FC_6H_4	β-glucopyranosyl-2,3,4,6-tetraacetate	S

Scheme 2



posed structure, which exhibits the presence of the methylene carbons (C-4, C-5) at δ 27.7, 28.9; the methyl carbon at δ 31.2 and the hetero C-3a, C-3 at δ 56.2, 66.1, respectively, in addition to the other skeletal carbons.

Similarly, the reaction of **2a, b** with 2,3,4,6-tetra-O-acetyl-β-D-glucopyranosylisothiocyanate afforded the corresponding glucopyranosylthiocarbamoyl derivatives **3q, r**. The structure of the latters was inferred from spectroscopic (IR, ^{1}H NMR, ^{13}C NMR and 2D-^{1}H, ^{1}H-Cosy) and elemental analyses data. The ^{1}H NMR spectra of **3q**, **r** reveal the glucose H-1 as a triplet signal. This is due to the coupling constant value between the glucose axial, axial interaction of H-1 and H-2 is equivalent to the coupling constant value between the glucose H-1 and the thiocarbamoyl NH proton. Upon addition of D_2O, the doublet thiocarbamoyl NH signal disappeared and the triplet glucose H-1 changed to a doublet signal. 2D-^{1}H, ^{1}H Cosy of **3q** as a representative example confirms the assignment of the structure (c.f. Experimental).

Reaction of **2** with acid anhydrides (maleic or succinic anhydride) afforded the corresponding acylating derivatives **4** and **5**. The olefinic protons of **4** were established to be of *cis*-configuration, this was supported by their coupling constant value in the ^{1}H NMR spectra (J = 12–13.4 Hz).

Reaction of **2** with either aliphatic (formic or acetic) or aromatic carboxylic acids (benzoic acid using dicyclohexylcarbodiimide as a dehydrating agent) afforded exclusively the 2-acyl-3-aryl-3,3a,4,5-tetrahydro-2*H*-benz[*g*]-indazoles **6a–d**.

2.2 Molluscicidal activity screening

Schistosomiasis is the most endemic trematode disease in tropical and subtropical regions. The intermediate host of *Schistosoma mansoni* which affects the intestinal system in man is called *Biomphalaria alexandrina* snail. The molluscicidal activity tests were carried out in accordance with the standard method [15, 16] by dissolving 0.1 g of the test compound in 10 ml acetone and adding the appropriate volume of that solution to 1 l of water to obtain the required concentration. Ten snails were used in each experiment. Reference experiments were carried out using the same volume of acetone added to 1 l of water. Exposure and recovery periods were 24 h each.

From the results (Table), it is obvious that many of the isolated compounds show remarkable molluscicidal activity. The best results were observed for the benzindazoles substituted at the 3-position with 4-methoxyphenylcarbamoyl (**3e, f**), methylthiocarbamoyl (**3j–m**) and ethylcarbamoyl (**3n**) moieties. Also, good results were observed for the formyl (**6a**) and acetyl (**6b, c**) derivatives bearing benzindazoles. The starting naphthalenones **1a–d** also revealed interesting molluscicidal activity.

3. Experimental

Melting points are uncorrected. IR spectra were recorded (KBr) on a Perkin Elmer 1650 spectrophotometer. ^{1}H NMR, ^{13}C NMR (APT) and 2D-^{1}H, ^{1}H Cosy were recorded on a Varian GEMINI 200 spectrometer (^{1}H : 200; ^{13}C : 50 MHz). The ^{13}C NMR spectrum of **3j** (decoupled and DEPT) was recorded on a JEOL EX 270 (67.5 MHz). The starting compounds **1a–d** were prepared according to previously reported procedures [17–20]. All

Table: Molluscicidal activity of the investigated compounds

Compd.	Number of snails out of 10 killed at a concentration of		
	20 ppm	10 ppm	5 ppm
1a	10	7	3
1b	10	9	6
1c	10	1	–
1d	10	7	–
3a	1	1	–
3b	2	–	–
3c	–	–	–
3d	1	–	–
3e	9	2	1
3f	10	3	1
3g	2	–	–
3h	1	–	–
3i	2	2	–
3j	10	8	2
3k	6	2	2
3l	10	1	1
3m	9	2	1
3n	10	10	3
3o	2	–	–
3p	7	–	–
3q	1	–	–
3r	1	–	–
4a	4	–	–
4b	1	–	–
4c	10	1	–
4d	3	–	–
5a	1	1	–
5b	2	–	–
5c	8	–	–
6a	10	10	7
6b	10	9	5
6c	9	3	1
6d	3	–	–

the results of elemental analyses were as expected and within acceptable limits.

3.1. 3-Aryl-3,3a,4,5-tetrahydro-2 H-benz[g]indazoles **2a–d** *(general procedure)*

A mixture of the appropriate **1** (10 mmol) and hydrazine hydrate (100%; 20 mmol) in EtOH (20 ml) was boiled under reflux for 3 h. Upon concentrating the reaction mixture (to about 1/2 of the initial volume) under reduced pressure and cooling the residue (−10 °C), colourless products were isolated, which were collected, washed with MeOH (5 ml) and used as quickly as possible without any further purification to avoid any decomposition.

3.2. 3-Aryl-2-substituted carbamoyl (or thiocarbamoyl)-3,3a,4,5-tetrahydro-2 H-benz[g]indazoles **3a–r** *(general procedure)*

A mixture of equimolar amounts of the appropriate **2** and aryl, alkyl isocyanate or isothiocyanate (5 mmol) in dry benzene (25 ml) containing TEA (3–5 drops) was boiled under reflux for the appropriate time. The solid separated upon concentrating the reaction mixture (≈10 ml). It was collected and crystallized from a suitable solvent affording the corresponding **3a–d**, **g**. In the case of **3f**, **i**, **k**, **o** after concentrating the reaction mixture to about 10 ml, light petroleum (40–60 °C) was added (≈15 ml). However, in the case of the other derivatives of **3** the reaction mixture was evaporated to dryness under reduced pressure, then the residue was triturated with MeOH or $(C_2H_5)_2O$ (5 ml). The corresponding **3e**, **h**, **j**, **l**, **m**, **p–r**; **3n** were separated respectively.

3.2.1. 2-(3,4-Dichlorophenylcarbamoyl)-3,3a,4,5-tetrahydro-3-(2-thienyl)-2 H-benz[g]indazole (**3a**)

Reaction time 5 h; crystallized from benzene-light petroleum (60–80 °C) mixture as 1 : 3 v/v (colourless crystals); m.p. 208–210 °C; yield 77%. IR : γ 3379 cm^{-1} (NH); 1693 (CO); 1575, 1515 (C=N, C=C). ^1H NMR ($CDCl_3$): δ 1.9–3.0 (m, 4 H, 2 CH_2); 3.37–3.52 (m, 1 H, hetero. H-3a); 5.25 (d, 1 H, hetero. H-3, J = 10.6 Hz); 6.99–8.0 (m, 10 H, arom. H); 8.24 (s, 1 H, NH). $C_{22}H_{17}Cl_2N_3OS$

3.2.2. 2-(3,4-Dichlorophenylcarbamoyl)-3-(4-fluorophenyl)-3,3a,4,5-tetrahydo-2 H-benz[g]indazole (**3b**)

Reaction time 20 h; crystallized from n-C_4H_9OH (colourless crystals); m.p. 193–194 °C; yield 84%. IR: ν 3374 cm^{-1} (NH); 1684 (CO); 1576, 1508 (C=N, C=C). ^1H NMR ($CDCl_3$): δ 1.9–3.03 (m, 4 H, 2 CH_2), 3.21–3.36 (m, 1 H, hetero. H-3a); 4.93 (d,1 H, hetero. H-3, J = 10.6 Hz); 7.05–8.02 (m, 11 H, arom. H); 8.25 (s, 1 H, NH).
$C_{24}H_{18}Cl_2FN_3O$

3.2.3. 3-(4-Chlorophenyl)-2-(3,4-dichlorophenylcarbamoyl)-3,3a,4,5-tetrahydro-2 H-benz[g]indazole (**3c**)

Reaction time 20 h; crystallized from n-C_4H_9OH (colourless crystals); m.p. 182–183 °C; yield 85%. IR: ν 3382 cm^{-1} (NH); 1681 (CO); 1579, 1522 (C=N, C=C). ^1H NMR ($CDCl_3$): δ 1.9–3.0 (m, 4 H, 2 CH_2); 3.2–3.34 (m, 1 H, hetero. H-3a); 4.92 (d, 1 H, hetero. H-3, J = 10.8 Hz), 7.2–8.0 (m, 11 H, arom. H); 8.24 (s, 1 H, NH).
$C_{24}H_{18}Cl_3N_3O$

3.2.4 2-(3,4-Dichlorophenylcarbamoyl)-3-(4-dimethylaminophenyl)-3,3a,4,5-tetrahydro-2 H-benz[g]indazole (**3d**)

Reaction time 25 h; crystallized from n-C_4H_9OH (yellow crystals); m.p. 214–216 °C; yield 79%. IR: ν 3382 cm^{-1} (NH); 1694 (CO); 1612, 1573 (C=N, C=C). ^1H NMR ($CDCl_3$): δ 1.85–3.05 [m, 10 H, 2 CH_2 + $N(CH_3)_2$]; 3.27–3.4 (m, 1 H, hetero. H-3a); 4.88 (d, 1 H, hetero. H-3, J = 10.6 Hz), 6.73–8.03 (m, 11 H, arom. H); 8.26 (s, 1 H, NH).
$C_{26}H_{24}Cl_2N_4O$

3.2.5. 2-(4-Methoxyphenylcarbamoyl)-3,3a,4,5-tetrahydro-3-(2-thienyl)-2 H-benz[g]indazole (**3e**)

Reaction time 20 h; crystallized from benzene-light petroleum (60–80 °C) mixture as 1:5 v/v (pale yellow crystals); m.p. 139–140 °C; yield 55%. IR: ν 3402 cm^{-1} (NH); 1692 (CO); 1593, 1512 (C=N, C=C). ^1H NMR ($CDCl_3$): δ 1.9–3.0 (m, 4 H, 2 CH_2); 3.37–3.51 (m, 1 H, hetero. H-3a); 3.78 (s, 3 H, OCH_3); 5.26 (d, 1 H, hetero. H-3, J = 10.6 Hz), 6.81–8.02 (m, 11 H, arom. H); 8.09 (s, 1 H, NH).
$C_{23}H_{21}N_3O_2S$

3.2.6. 3-(4-Fluorophenyl)-2-(4-methoxyphenylcarbamoyl)-3,3a,4,5-tetrahydro-2 H-benz[g]indazole (**3f**)

Reaction time 30 h; crystallized from EtOH (colourless crystals); m.p. 165–166 °C; yield 64%. IR: ν 3356 cm^{-1} (NH); 1682 (CO); 1596, 1532 (C=N, C=C). ^1H NMR ($CDCl_3$): δ 1.9–2.99 (m, 4 H, 2 CH_2); 3.2–3.35 (m, 1 H, hetero. H-3a); 3.77 (s, 3 H, OCH_3); 4.94 (d, 1 H, hetero. H-3, J = 11 Hz); 6.8–8.03 (m, 12 H, arom. H); 8.09 (s, 1 H, NH).
$C_{25}H_{22}FN_3O_2$

3.2.7. 3-(4-Chlorophenyl)-2-(4-methoxyphenylcarbamoyl)-3,3a,4,5-tetrahydro-2 H-benz[g]indazole (**3g**)

Reaction time 25 h; crystallized from n-C_4H_9OH (colourless crystals); m.p. 172–173 °C; yield 65%. IR: ν 3398 cm^{-1} (NH); 1675 (CO); 1596, 1528 (C=N, C=C). ^1H NMR ($CDCl_3$): δ 1.9–3.0 (m, 4 H, 2 CH_2); 3.18–3.3 (m, 1 H, hetero. H-3a); 3.77 (s, 3 H, OCH_3); 4.92 (d, 1 H, hetero. H-3, J = 11 Hz), 6.78–8.04 (m, 12 H, arom. H); 8.08 (s, 1 H, NH).
$C_{25}H_{22}ClN_3O_2$

3.2.8. 2-Phenylthiocarbamoyl-3,3a,4,5-tetrahydro-3-(2-thienyl)-2 H-benz[g]-indazole (**3h**)

Reaction time 70 h; crystallized from n-C_4H_9OH (almost colourless crystals); m.p. 185–187 °C; yield 74%. IR: ν 3315 cm^{-1} (NH); 1593, 1519, 1443 (C=N, C=C, C=S). ^1H NMR ($CDCl_3$): δ 1.95–3.02 (m, 4 H, 2 CH_2); 3.41–3.54 (m, 1 H, hetero. H-3a); 5.79 (d, 1 H, hetero. H-3, J = 8.2 Hz), 6.98–8.01 (m, 12 H, arom. H); 9.41 (s, 1 H, NH).
$C_{22}H_{19}N_3S_2$

3.2.9. 3-(4-Fluorophenyl)-2-phenylthiocarbamoyl-3,3a,4,5-tetrahydro-2 H-benz[g]indazole (**3i**)

Reaction time 70 h; crystallized from n-C_4H_9OH (almost colourless crystals); m.p. 190–192 °C; yield 65%. IR: ν 3323 cm^{-1} (NH); 1598, 1516, 1463 (C=N, C=C, C=S). ^1H NMR ($CDCl_3$): δ 1.95–3.02 (m, 4 H, 2 CH_2); 3.24–3.37 (m, 1 H, hetero. H-3a); 5.46 (d, 1 H, hetero. H-3, J = 8.4 Hz), 7.01–8.02 (m, 13 H, arom. H); 9.42 (s, 1 H, NH).
$C_{24}H_{20}FN_3S$

3.2.10. 2-Methylthiocarbamoyl-3,3a,4,5-tetrahydro-3-(2-thienyl)-2 H-benz[g]indazole (**3j**)

Reaction time 60 h; crystallized from n-C_4H_9OH (colourless crystals); m.p. 172–173 °C; yield 81%. IR: ν 3301 cm^{-1} (NH); 1598, 1516, 1460 (C=N, C=C, C=S). ^1H NMR ($CDCl_3$): δ 1.9–2.99 (m, 4 H, 2 CH_2); 3.18 (d, 3 H, CH_3, J = 5 Hz); 3.32–3.46 (m, 1 H, hetero. H-3a); 5.65 (d, 1 H, hetero. H-3, J = 8.8 Hz); 6.96–7.93 (m, 8 H, 7 arom. H + NH). ^{13}C NMR ($CDCl_3$): 27.7, 28.9 (hetero. C-4, C-5); 31.2 (CH_3); 56.2 (hetero. C-3a); 66.1 (hetero. C-3); 123.6; 123.9, 124.6, 126.6, 129.0, 130.5 (6 CH, arom. CH); 126.5, 139.5, 146.8, 154.9 (4 C, arom. quaternary C); 179.7 (CS).
$C_{17}H_{17}N_3S_2$

3.2.11. 3-(4-Fluorophenyl)-2-methylthiocarbamoyl-3,3a,4,5-tetrahydro-2 H-benz[g]indazole (**3k**)

Reaction time 60 h; crystallized from n-C_4H_9OH (almost colourless crystals); m.p. 196–197 °C; yield 77%. IR: ν 3367 cm^{-1} (NH); 1601, 1511, 1465 (C=N, C=C, C=S). ^1H NMR ($CDCl_3$): δ 1.9–2.98 (m, 4 H, 2 CH_2); 3.17 (d, 3 H, CH_3, J = 4.8 Hz), 3.11–3.29 (m, 1 H, hetero. H-3a); 5.34 (d, 1 H, hetero. H-3, J = 8.8 Hz); 6.99–7.95 (m, 9 H, 8 arom. H + NH).
$C_{19}H_{18}FN_3S$

3.2.12. 3-(4-Chlorophenyl)-2-methylthiocarbamoyl-3,3a,4,5-tetrahydro-2 H-benz[g]indazole (**3l**)

Reaction time 55 h; crystallized from n-C_4H_9OH (almost colourless crystals); m.p. 182–184 °C; yield 68%. IR: ν 3362 cm^{-1} (NH); 1601, 1519, 1488 (C=N, C=C, C=S). ^1H NMR ($CDCl_3$): δ 1.9–2.98 (m, 4 H, 2 CH_2); 3.17 (d, 3 H, CH_3, J = 4.8 Hz); 3.12–3.28 (m, 1 H, hetero. H-3a); 5.32 (d, 1 H, hetero. H-3, J = 9 Hz); 7.18–7.94 (m, 9 H, arom. H + NH).
$C_{19}H_{18}ClN_3S$

3.2.13. 3-(4-Dimethylaminophenyl)-2-methylthiocarbamoyl-3,3a,4,5-tetrahydro-2 H-benz[g]indazole (**3m**)

Reaction time 65 h; crystallized from MeOH (colourless crystals); m.p. 138–139 °C; yield 71%. IR: ν 3377 cm^{-1} (NH); 1615, 1519, 1463 (C=N, C=C, C=S). ^1H NMR ($CDCl_3$): δ 1.9–2.94 [m, 10 H, 2 CH_2 +$N(CH_3)_2$]; 3.17 (d, 3 H, CH_3, J = 5 Hz); 3.21–3.34 (m, 1 H, hetero. H-3a); 5.28 (d, 1 H, hetero. H-3, J = 8.6 Hz), 6.72–7.95 (m, 9 H, 8 arom. H + NH).
$C_{21}H_{24}N_4S$

3.2.14. 2-Ethylcarbamoyl-3,3a,4,5-tetrahydro-3-(2-thienyl)-2 H-benz[g]-indazole (**3n**)

Reaction time 50 h; crystallized from cyclohexane (pale yellow crystals); m.p. 125–126 °C; yield 38%. IR: ν 3355 cm^{-1} (NH); 1657 (CO); 1597, 1511 (C=N, C=C). ^1H NMR ($CDCl_3$): δ 1.19 (t, 3 H, CH_3, J = 7.4 Hz);

1.88–3.0 (m, 4 H, 2 CH_2); 3.26–3.45 (m, 3 H, hetero. H-3a + $C\underline{H}_2-CH_3$); 5.7 (d, 1 H, hetero. H-3, J = 11 Hz); 6.16 (t, 1 H, NH, J = 5.6 Hz); 6.96–7.96 (m, 7 H, arom. H).
$C_{18}H_{19}N_3OS$

3.2.15. 2-Ethylthiocarbamoyl-3,3a,4,5-tetrahydro-3-(2-thienyl)-2H-benz[g]-indazole (**3o**)

Reaction time 65 h; crystallized from n-C_4H_9OH (pale yellow crystals); m.p. 171–172 °C; yield 59%. IR: ν 3299 cm^{-1} (NH); 1615, 1512, 1460 (C=N, C=C, C=S). ^1H NMR ($CDCl_3$): δ 1.28 (t, 3 H, CH_3, J = 7.4 Hz); 1.9–2.99 (m, 4 H, 2CH_2); 3.31–3.45 (m, 1 H, hetero. H-3a); 3.62–3.75 (m, 2 H, $C\underline{H}_2CH_3$); 5.66 (d, 1 H, hetero. H-3, J = 8.8 Hz); 6.96–7.95 (m, 8 H, 7 arom. H + NH).
$C_{18}H_{19}N_3S_2$

3.2.16. 2-Ethylthiocarbamoyl-3-(4-fluorophenyl)-3,3a,4,5-tetrahydro-2 H-benz[g]indazole (**3p**)

Reaction time 65 h; crystallized from cyclohexane (almost colourless crystals); m.p. 175–177 °C; yield 34%. IR: ν 3356 cm^{-1} (NH); 1601, 1508, 1463 (C=N, C=C, C=S). ^1H NMR ($CDCl_3$): δ 1.27 (t, 3 H, CH_3, J = 7.2 Hz); 1.9–2.98 (m, 4 H, 2 CH_2); 3.15–3.28 (m, 1 H, hetero. H-3a); 3.6–3.73 (m, 2 H, $C\underline{H}_2CH_3$); 5.34 (d, 1 H, hetero. H-3, J = 8.6 Hz), 6.96–7.95 (m, 9 H, arom. H + NH).
$C_{20}H_{20}FN_3S$

3.2.17. 2[(2,3,4,6-Tetra-O-acetyl-β-glucopyranosyl)thiocarbamoyl]-3,3a,4,5-tetrahydro-3-(2-thienyl)-2 H-benz[g]indazole (**3q**)

Reaction time 70 h; crystallized from EtOH (colourless crystals); m.p. 130–132 °C; yield 42%. IR: ν 3531, 3363 cm^{-1} (NH); 1751 (CO); 1525, 1461, 1372 (C=N, C=C, C=S). ^1H NMR ($CDCl_3$): δ 1.9–2.98 (m, 16 H, 4 $COCH_3$ + hetero. 2 CH_2); 3.3–3.45 (m, 1 H, hetero. H-3a); 3.86 (ddd, 1 H, gluc. H-5, J = 2.2, 4.4, 10 Hz); 4.09 (dd, 1 H, upfield H of gluc. H-6, J = 2.2, 12.6 Hz); 4.3 (dd, 1 H, downfield H of gluc. H-6, J = 4.4, 12.4 Hz); 5.11 (t, 1 H, gluc. H-4, J = 9.4 Hz); 5.16 (t, 1 H, gluc. H-2, J = 9.6 Hz); 5.36 (t, 1 H, gluc. H-3, J = 9.4 Hz); 5.57 (d, 1 H, hetero. H-3, J = 8 Hz); 5.76 (t, 1 H, gluc. H-1, J = 9.4 Hz); 6.94–7.98 (m, 7 H, arom. H); 8.23 (d, 1 H, NH, J = 9.2 Hz). ^{13}C NMR ($CDCl_3$): δ 20.8–21.0 (CH_3); 28.1, 29.4 (hetero. C-4, C-5); 56.8 (hetero. C-3a); 62.1 (gluc. C-6); 66.6 (hetero. C-3); 68.7, 71.0, 73.3, 73.7, 82.7 (gluc. C-4, C-2, C-3, C-5, C-1 respectively); 124.8, 126.0, 127.4; 129.6, 131.7 (5 CH, arom.CH); 126.9, 140.3, 146.7, 157.1 (4 C, arom. quaternary C); 170.3, 170.6, 171.3, 171.5 (4 CO); 179.4 (CS).
$C_{30}H_{33}N_3O_9S_2$

3.2.18. 3-(4-Fluorophenyl)-2-[(2,3,4,6-tetra-O-acetyl-β-glucopyranosyl)-thiocarbamoyl]-3,3a,4,5-tetrahydro-2 H-benz[g]indazole (**3r**)

Reaction time 70 h; crystallized from EtOH (colourless crystals); m.p. 228–230 °C; yield 71%. IR: ν 3545, 3367 cm^{-1} (NH); 1749 (CO); 1604, 1516, 1460 (C=N, C=C, C=S). ^1H NMR ($CDCl_3$): δ 1.91–2.97 (m, 16 H, 4 $COCH_3$ + hetro. 2 CH_2); 3.15–3.28 (m, 1 H, hetero. H-3a); 3.85 (ddd, 1 H, gluc. H-5, J = 2.2, 4.4, 9.8 Hz); 4.09 (dd, 1 H, upfield H of gluc. H-6, J = 2.2, 12.6 Hz); 4.29 (dd, 1 H, downfield H of gluc. H-6, J = 4.6, 12.4 Hz); 5.1 (t, 1 H, gluc. H-4, J = 9.2 Hz); 5.15 (t, 1 H, gluc. H-2, J = 9.4 Hz); 5.26 (d, 1 H, hetero. H-3, J = 8.2 Hz); 5.35 (t, 1 H, gluc. H-3, J 9.2 Hz); 5.73 (t, 1 H, gluc. H-1, J 9.2 Hz); 6.98–7.99 (m, 8 H, arom. H); 8.22 (d, 1 H, NH, J = 9.2 Hz).
$C_{32}H_{34}FN_3O_9S$

3.3. 1-(3-Aryl-3,3a,4,5-tetrahydro-2 H-benz[g]indazole-2-yl)maleic acids **4a–d** *(general procedure)*

A solution of equimolar amounts of maleic anhydride (5 mmol) in dry THF (10 ml) was added dropwise to a solution of the appropriate **2** in dry THF (10 ml). The reaction mixture was stirred at room temperature (20–25 °C) for the appropriate time. The separated solid was collected and crystallized from a suitable solvent affording the corresponding **4a**, **b**, **d**. In the case of **4c**, the reaction mixture was evaporated to dryness under reduced pressure and the residue was triturated with MeOH giving rise to **4c**.

3.3.1. 1-[3,3a,4,5-Tetrahydro-3-(2-thienyl)-2 H-benz[g]indazole-2-yl]maleic acid (**4a**)

Reaction time 24 h; crystallized from n-C_4H_9OH (yellow crystals); m.p. 181–183 °C; yield 80%. IR: ν 3631 cm^{-1} (OH); 1703 (CO);1621, 1601 (C=N, C=C). ^1H-NMR ($CDCl_3$): δ 1.9–3.05 (m, 4 H, 2 CH_2); 3.46–3.59 (m, 1 H, hetero. H-3a); 5.42 (d, 1 H, hetero. H-3, J = 8.4 Hz); 6.45 (d, 1 H, olefinic CH, J =13.4 Hz); 6.99–8.0 (m, 9 H, 7 arom. H + olefinic CH + OH).
$C_{19}H_{16}N_2O_3S$

3.3.2. 1-[3-(4-Fluorophenyl)-3,3a,4,5-tetrahydro-2 H-benz[g]indazole-2-yl]-maleic acid (**4b**)

Reaction time 24 h; crystallized from n-C_4H_9OH (pale yellow crystals); m.p. 200–202 °C; yield 77%. IR: γ 3652 cm^{-1} (OH); 1709 (CO); 1616, 1546 (C=N, C=C). ^1H NMR ([D6]DMSO): δ 1.85–3.01 (m, 4 H, 2 CH_2); 3.2–3.33 (m, 1 H, hetero. H-3a); 5.06 (d, 1 H, hetero. H-3, J = 9.6 Hz); 6.26 (d, 1 H, olefinic CH, J = 12 Hz); 6.9 (d, 1 H, olefinic CH, J = 12 Hz); 7.19–7.85 (m, 9 H, 8 arom. H + OH).
$C_{21}H_{17}FN_2O_3$

3.3.3. 1-[3-(4-Chlorophenyl)-3,3a,4,5-tetrahydro-2 H-benz[g]indazole-2-yl]-maleic acid (**4c**)

Reaction time 48 h; crystallized from n-C_4H_9OH (almost colourless crystals); m.p. 191–193 °C; yield 84%. IR: ν 3406 cm^{-1} (OH); 1710 (CO); 1620, 1553 (C=N, C=C). ^1H NMR ($CDCl_3$): δ 1.9–3.03 (m, 4 H, 2 CH_2); 3.27–3.4 (m, 1 H, hetero. H-3a); 5.06 (d, 1 H, hetero. H-3, J = 8.6 Hz); 6.44 (d, 1 H, olefinic CH, J = 13.2 Hz); 7.22–8.0 (m, 10 H, 8 arom. H + olefinic CH + OH).
$C_{21}H_{17}ClN_2O_3$

3.3.4. 1-[3-(4-Dimethylaminophenyl)-3,3a,4,5-tetrahydro-2 H-benz[g]-indazole-2-yl]maleic acid (**4d**)

Reaction time 24 h; crystallized from benzene-light petroleum (60–80 °C) mixture as 1:1 v/v; m.p. 188–190 °C; yield 87%. IR: ν 3384 cm^{-1} (OH); 1712 (CO); 1617, 1553 (C=N, C=C). ^1H NMR ($CDCl_3$): δ 1.9–3.07 [m, 10 H, 2 CH_2 + $N(CH_3)_2$]; 3.3–3.46 (m, 1 H, hetero. H-3a); 5.01 (d, 1 H, hetero. H-3, J = 8.2 Hz); 6.42 (d, 1 H, olefinic CH, J = 13.2 Hz); 6.7–8.02 (m, 10 H, 8 arom. H + olefinic CH + OH).
$C_{23}H_{23}N_3O_3$

3.4. 1-(3-Aryl-3,3a,4,5-tetrahydro-2 H-benz[g]indazole-2-yl)succinic acids **5a–c** *(general procedure)*

A solution of equimolar amounts of succinic anhydride (5 mmol) in dry THF (15 ml) was added dropwise to a solution of the appropriate **2** in dry THF (10 ml). The reaction mixture was stirred at room temperature (20–25 °C) for the appropriate time. Then, the reaction mixture was evaporated to dryness under reduced pressure, the residue was triturated with $(C_2H_5)_2O$ or MeOH (5 ml), the separated solid was collected and crystallized from a suitable solvent affording the corresponding **5a**; **5b**, **c** respectively.

3.4.1. 1-[3,3a,4,5-Tetrahydro-3-(2-thienyl)-2 H-benz[g]indazole-2-yl]-succinic acid (**5a**)

Reaction time 24 h; crystallized from benzene-light petroleum (60–80 °C) mixture as 1:1 v/v (pale yellow crystals); m.p. 143–145 °C; yield 68%. IR: ν 3150–2570 cm^{-1} (OH); 1706 (CO); 1666, 1614 (C=N, C=C). ^1H NMR ($CDCl_3$): δ 1.9–3.19 (m, 8 H, hetero. 2 CH_2 + 2 $COCH_2$); 3.32–3.46 (m, 1 H, hetero. H-3a); 5.28 (d, 1 H, hetero. H-3, J = 9.6 Hz); 6.94–8.0 (m, 7 H, arom. H); 9.8 (br., 1 H, OH).
$C_{19}H_{18}N_2O_3S$

3.4.2. 1-[3-(4-Fluorophenyl)-3,3a,4,5-tetrahydro-2 H-benz[g]indazole-2-yl]-succinic acid (**5b**)

Reaction time 48 h; crystallized from MeOH (85%) (colourless crystals); m.p. 162–164 °C; yield 66%. IR: ν 3570 cm^{-1} (OH); 1703 (CO); 1657, 1606 (C=N, C=C). ^1H NMR ($CDCl_3$): δ 1.85–3.27 [m, 9 H, hetero. 2 CH_2 + 2 $COCH_2$ + hetero. H-3a); 4.95 (d, 1 H, hetero. H-3, J = 9.4 Hz); 7.0–8.0 (m, 8 H, arom. H); 9.6 (br., 1 H, OH).
$C_{21}H_{19}FN_2O_3$

3.4.3. 1-[3-(4-Chlorophenyl)-3,3a,4,5-tetrahydro-2 H-benz[g]indazole-2-yl]-succinic acid (**5c**)

Reaction time 48 h; crystallized from n-C_4H_9OH-light petroleum (60–80 °C) mixture as 1:5 v/v (colourless crystals); m.p. 192–193 °C; yield 73%. IR: ν 3250–2580 cm^{-1} (OH); 1703 (CO); 1664, 1610 (C=N, C=C). ^1H NMR ([D_6]DMSO): δ 1.85–3.37 (m, 9 H, hetero. 2 CH_2 + 2 $COCH_2$ + hetero. H-3a); 4.98 (d, 1 H, hetero. H-3, J = 9.8 Hz); 7.26–7.91 (m, 8 H, arom. H); 12.1 (br., 1 H, OH).
$C_{21}H_{19}ClN_2O_3$

3.5. 2-Acyl-3-aryl-3,3a,4,5-tetrahydro-2 H-benz[g]indazoles **6a–c** *(general procedure)*

A solution of the appropriate **2** (5 mmol) in the corresponding aliphatic carboxylic acid (formic 98% or glacial acetic acid) (25 ml) was boiled under reflux for 12 h. After cooling, the reaction mixture was poured into ice-cold H_2O (200 ml). The solid separated was collected and crystallized from a suitable solvent affording the corresponding **6b**, **c**. In the case of

6a the oily mass formed upon pouring the reaction mixture into H_2O, was decanted and triturated with MeOH (5 ml), so, the corresponding **6a** was isolated.

3.5.1. 3-(4-Fluorophenyl)-2-formyl-3,3a,4,5-tetrahydro-2 H-benz[g]indazole (**6a**)

Crystallized from MeOH (colourless crystals); m.p. 164–166 °C; yield 61%. IR: ν 1653 cm^{-1} (CO); 1608, 1508 (C=N, C=C). ^1H NMR ($CDCl_3$): δ 0.95–3.0 (m, 4 H, 2 CH_2); 3.55–3.7 (m, 1 H, hetero. H-3 a); 5.65 (d, 1 H, hetero. H-3, J = 11 Hz); 6.96–8.07 (m, 8 H, arom. H); 8.98 (s, 1 H, CHO). $C_{18}H_{15}FN_2O$

3.5.2. 2-Acetyl-3-(4-fluorophenyl-3,3a,4,5-tetrahydro-2 H-benz[g]indazole (**6b**)

Crystallized from MeOH (colourless crystals); m.p. 162–164 °C; yield 79%. IR: ν 1653 cm^{-1} (CO); 1604, 1511 (C=N, C=C). ^1H NMR ($CDCl_3$): δ 1.85–2.99 (m, 7 H, 2 CH_2 + CH_3); 3.14–3.28 (m, 1 H, hetero. H-3 a); 4.95 (d, 1 H, hetero. H-3, J = 9.6 Hz); 7.0–8.0 (m, 8 H, arom. H). $C_{19}H_{17}FN_2O$

3.5.3. 2-Acetyl-3-(4-chlorophenyl)-3,3a,4,5-tetrahydro-2 H-benz[g]indazole (**6c**)

Crystallized from MeOH (colourless crystals); m.p. 176–177 °C; yield 71%. IR: ν 1657 cm^{-1} (CO); 1612, 1491 (C=N, C=C). ^1H NMR ($CDCl_3$): δ 1.85–2.99 (m, 7 H, 2 CH_2 + CH_3); 3.13–3.26 (m, 1 H, hetero. H-3 a); 4.93 (d, 1 H, hetero. H-3, J = 9.4 Hz); 7.18–8.0 (m, 8 H, arom. H). $C_{19}H_{17}ClN_2O$

3.6. 2-Benzoyl-3-(4-chlorophenyl)-3,3a,4,5-tetrahydro-2 H-benz[g]indazole (***6d***)

A solution of DCC (5 mmol) in dry TFH (10 ml) was added dropwise to a cold solution (5 °C) of equimolar amounts of benzoic acid (5 mmol) and the corresponding **2c** in dry THF (10 ml). After the addition was completed, the reaction mixture was stirred at room temperature (24 °C) for 96 h. The colourless solid separated was collected and identified as 1,3-dicyclohexylurea (m.p. 234–236 °C; yield 55%). The remaining reaction mixture was evaporated to dryness under reduced pressure and the residue was triturated with $(C_2H_5)_2O$ (5 ml), the separated solid was collected (**6d**) and crystallized from EtOH (colourless crystals); m.p. 207–209 °C; yield 52%. IR: ν 1630 cm^{-1} (CO); 1613, 1575 (C=N, C=C). ^1H NMR ($CDCl_3$): δ 1.9–2.97 (m, 4 H, 2 CH_2); 3.19–3.33 (m, 1 H, hetero. H-3 a); 5.16 (d, 1 H, hetero. H-3, J = 10.2 Hz); 7.16–8.04 (m, 13 H, arom. H). $C_{24}H_{19}ClN_2O$.

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References

1 Yousif, N. M.; Gad, F. A.; Hassanien, H.: Egypt. J. Pharm. Sci. **37**, 145 (1996)
2 Cantegril, R.; Croisat, D.; Desbordes, P.; Guigues, F.; Mortier, J.; Peignier, R.; Vors, J. P.: (Rhone Poulenc Agrochimie) 11 Nov. 1993 (Cl. C07D231/12); C.A. **120**, 270382 (1994)
3 Ditrich, K.; Hamprecht, G.; Wuerzer, B.; Meyer, N.; Westphalen, K. O.; Laatsch, H.: (BASF A.-G.) 29 Mar. 1990 (Cl. C07D231/54); C.A. **113**, 152403 (1990)
4 Rogers, R. S.; Talley, J. J.; Bertenshaw, S. R.: (G. D. Searle & Co., USA) 28 Mar. 1996 (Cl. C07D231/54); C.A. **125**, 114604 (1996)
5 Kumar, V.; Bell, M. R.; Wetzel, J. R.; Herrmann, J. L.; McGarry, R.; Schane, H. P.; Winneker, R. C.; Snyder, B. W.; Anzalone, A. J.: J. Med. Chem. **36**, 3278 (1993)
6 Wichmann, J.: (F. Hoffmann-La Roche Ag, Switz.) 13 Feb. 1996 (Cl. C07D231/54); C.A. **124**, 343294 (1996)
7 Connolly, P. J.; Wachter, M. P.: (Ortho Pharmaceutical Corp.) 7 Feb. 1995 (Cl. 548-360.1; C07D231/54); C.A. **122**, 265369 (1995)
8 Harrison, C. R.; Lett, R. M.; McCann, S. F.; Shapiro, R.; Stevenson, T. M.: (E.I. Du Pont de Nemours and Company) 12 Dec. 1995 (Cl. 514–254; C07D401/04); C.A. **124**, 202246 (1996)
9 Harrison, G. R.; Lett, R. M.; McCann, S. F.; Shapiro, R.; Stevenson, T. M.: (du Pont de Nemours, E.I., and Co.) 5 Mar. 1992 (Cl. C07D231/54); C.A. **117**, 26559 (1992)
10 Lahm, G. P.: (du Pont de Nemours, E.I., and Co.) 25 Apr. 1990 (Cl. C07D231/54); C.A. **113**, 191341 (1990)
11 Fahmy, M. A. H.; Harrison, C. R.; Lahm, G. P.; Stevenson, T. M.: (du Pont de Nemours, E.I., and Co.) 5 Apr. 1990 (Cl. C07D231/06); C.A. **113**, 172010 (1990)
12 Lahm, G. P.: (du Pont de Nemours, E.I., and Co.) 12 Oct. 1988 (Cl. C07D231/54); C.A. **110**, 95229 (1989)
13 Mishriky, N.; Asaad, F. M.; Ibrahim, Y. A.; Girgis, A. S.: Pharmazie **51**, 544 (1996)
14 Grant, N.; Mishriky, N.; Asaad, F. M.; Fawzy, N. G.: Pharmazie **53**, 543 (1998)
15 World Health Organization: Wld. Hlth. Org. **65**, 33 (1953)
16 World Health Organization: Bull. Wld. Hlth. Org. **33**, 567 (1956)
17 Cagniant, P.; Cagniant, P. Mme: Bull. Soc. Chim. France 713 (1952)
18 Azzolina, O.; Desimoni, G.; Di Toro, V.; Ghislandi, V.; Tacconi, G.: Gazz. Chim. Ital. **105**, 971 (1975)
19 El-Rayyes, N. R.; Al-Jawhary, A.: J. Heterocyclic Chem. **23**, 135 (1986)
20 Shriner, R. L.; Teeters, W. O.: J. Am. Chem. Soc. **60**, 936 (1938)

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