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Synthesis of some triazolyl-benzofuranamine derivatives

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Abstract

The synthesis of some triazoly-benzofuranamine derivatives starting from 2-chloro-*N*-(5-substituted-2,3-dihydro-3-benzofuryl)acetamides and 3-(aryloxyalkyl)-4-ethyl/phenyl-5-mercapto-1,2,4-triazoles is described. The chemical structures of the compounds were elucidated. The prepared compounds were tested for herbicidal activity.

Keywords: Triazolyl-benzofuranamine; Herbicidal activity

1. Introduction

Benzofurane derivatives present some interesting biological activities [1–4]. Various benzofuranamine derivatives showed the herbicidal activity [5].

Triazol derivatives have been extensively studied and possessed a broad spectrum of biological activities [6–8].

In this work, we have synthesized some triazolyl-benzofuranamine derivatives and the prepared compounds were tested for phytotoxicity in vitro and in the greenhouse tests by Aventis (RHONE-POULENC).

2. Chemistry

In this work; 2-chloro-*N*-(5-substituted-2,3-dihydro-3-benzofuryl)acetamides (**1**) were prepared for the first time in accordance with the method described in literature [9].

3-(Aryloxyalkyl)-4-ethyl/phenyl-5-mercapto-1,2,4-triazoles (**2**) were synthesized in according to a reported procedure [10,11].

The reaction of 2-chloro-acedamide (**1**), triazole(**2**) and anhydrous potassium carbonate in acetone gave the 3-[5-(substitutedphenoxyalkyl)-4-ethyl/phenyl-1,2,4-triazole-3-yl)thio-acetylamino]-5-substitued-2,3-dihydrobenzofurane (**3a–q**) (Scheme 1).

Analytical and spectral data (IR, ^{1}H NMR, MS-(FAB$^+$)) confirmed the structure of the compounds.

3. Experimental

3.1. Chemistry

Melting points were determined by using a Gallenkamp apparatus and are uncorrected. Spectroscopic data were recorded by the following instruments. IR: Shimadzu 435 spectrophotometer; ^{1}H NMR: Bruker 250 MHz spectrometer, MS: VG Quattro mass spectrometer.

3.1.1. General procedure for the synthesis of the compounds

*3.1.1.1. 2-Chloro-N-(5-substituted-2,3-dihydro-3-benzofuryl)acetamides (**1**).* This compound was prepared by reacting 3-aminobenzofurane (0.1 mol) with chloroacetylchloride (0.1 mol) in toluene. The reaction was catalyzed by triethylamine (0.1 mol).

*3.1.1.2. 3-(Aryloxyalkyl)-4-ethyl/phenyl-5-mercapto-1,2,4-triazoles (**2**).* Suitable substituted thiosemicarbazides (*N*-(alkyl/phenyl)-*N*′-aryloxyalkyl-thiosemicarbazide) (0.02 mol) were dissolved in 2 N NaOH and the resulting solution was heated under reflux for 3 h. The solution was cooled and acidified to pH 2–3 with water and recrystallized from EtOH.

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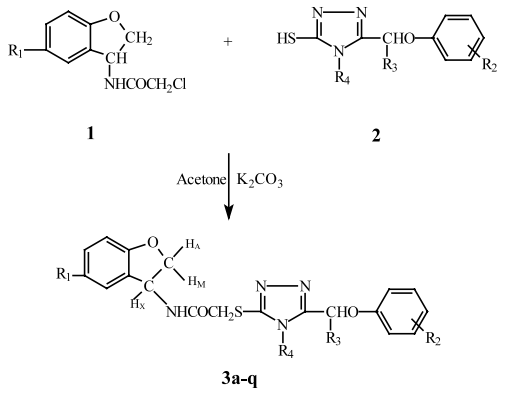

Scheme 1.

*3.1.1.3. 3-[5-(substitutedphenoxyalkyl)-4-ethyl/phenyl-1,2,4-triazole-3-yl)thioacetylamino]-5-substituted-2,3-dihydrobenzofurane (**3a–q**).* To a suspension of acetamide (**1**) (0.005 mol) in acetone (10 ml), was added an equimolar amount of triazole (**2**). An equimolar K_2CO_3 was added as a catalyst and the solution was stirred for 10 h. The solid was evaporated. The residue was dispersed with water to obtain triazolyl-benzofurane (**3a–q**) (Table 1).

3a: IR (KBr, cm^{-1}): 3250 (N–H), 1675 (CONH), 1572 (C=N), 1240 (C–O–C). ^1H NMR (250 MHz, DMSO-d_6, δ ppm): 1.25 (3H, t, $J = 7.2$ Hz, CH_3–C), 2.1 (3H, s, CH_3–Ar), 3.90 (2H, s, $COCH_2S$), 4.05 (2H, q, N–CH_2), 4.20 (1H, q, H_A), 4.65 (1H, t, H_M), 5.20 (2H, s, CH_2O), 5.40 (1H, m, H_X), 6.70–7.40 (7H, m, Ar–H), 8.95 (1H, d, $J = 6.8$ Hz), NHCO).

3d: IR (KBr, cm^{-1}): 3280 (N–H), 1670 (CONH), 1570 (C=N), 1260 (C–O–C). ^1H NMR (250 MHz, DMSO-d_6, δ ppm): 1.35 (3H, t, CH_3–C), 2.30 (3H, s, CH_3–Ar), 4.00 (2H, s, $COCH_2$), 4.10 (2H, q, N–CH_2), 4.25 (1H, q, H_A), 4.70 (1H, t, H_M), 5.25 (2H, s, OCH_2), 5.50 (1H, m, H_X), 6.80–7.40 (7H, m, Ar–H), 8.95 (1H, d, $J = 7.00$ Hz, NHCO).

3i: IR (KBr, cm^{-1}): 3320 (N–H), 1655 (CONH), 1572 (C=N), 1210 (C–O–C). ^1H NMR (250 MHz, DMSO-d_6, δ ppm): 1.82 (3H, d, CH_3), 4.00 (2H, s, $COCH_2$), 4.25 (1H, q, H_A), 4.70 (1H, t, H_M), 5.25 (1H, m, CH–O), 5.50 (1H, m, H_X), 6.80–7.65 (12H, m, Ar–H), 9.00 (1H, d, $J = 7.00$ Hz, NHCO).

3k: IR (KBr, cm^{-1}): 3275 (N–H), 1665 (CONH), 1570 (C=N), 1245 (C–O–C). ^1H NMR (250 MHz, DMSO-d_6, δ ppm): 1.25 (3H, t, $J = 7.20$ Hz), CH_3–C), 3.65 (3H, s, OCH_3), 3.95 (2H, s, $COCH_2$), 4.00 (2H, m, N–CH_2), 4.15 (1H, q, H_A), 4.55 (1H, t, H_M), 5.30 (2H, s, OCH_2), 5.40 (1H, m, H_X), 6.60–7.50 (7H, m, Ar–H), 8.85 (1H, d, $J = 7.30$ Hz, NHCO).

3l: IR (KBr, cm^{-1}): 3265 (N–H), 1670 (CONH), 1571 (C=N), 1250 (C–O–C). ^1H NMR (250 MHz, DMSO-d_6, δ ppm): 1.30 (3H, t, CH_3–C), 2.20 (3H, s, CH_3–Ar), 3.70 (3H, s, OCH_3), 3.90 (2H, s, $COCH_2$), 4.00 (2H, q, N–CH_2), 4.15 (1H, q, H_A), 4.6 (1H, t, H_M), 5.25 (2H, s, OCH_2), 5.40 (1H, m, H_X), 6.70–7.20 (7H, m, Ar–H), 6.95 (2H, d, $J = 8.50$ Hz), C_3–H, C_5–H of phenyl), 7.10 (2H, d, $J = 8.50$ Hz), C_2–H, C_6–H of phenyl), 8.85 (1H, d, $J = 7.10$ Hz), NHCO).

3q: IR (KBr, cm^{-1}): 3245 (N–H), 1665 (CONH), 1570 (C=N), 1240 (C–O–C). ^1H NMR (250 MHz, DMSO-d_6, δ ppm): 1.55 (3H, d, $J = 6.44$ Hz), CH_3–C), 3.65 (3H, s, OCH_3), 3.90 (2H, s, $COCH_2$), 4.15 (1H, q, H_A), 4.55 (1H, t, H_M), 5.40 (1H, m, H_X), 5.50 (1H, q, CH–O), 6.60–7.55 (12H, m, Ar–H), 8.85 (1H, d, $J =$ 7.10 Hz), NHCO). MS (FAB) $[M + 1]$: m/z 537.

Table 1
Some characteristics of the compounds

Comp.	R_1	R_2	R_3	R_4	M.p. (°C)	Yield (%)	Molecular formula
3a	Cl	2-CH_3	H	C_2H_5	65	78	$C_{22}H_{23}ClN_4O_3S$
3b	Cl	2-Cl	H	C_2H_5	73	78	$C_{21}H_{20}Cl_2N_4O_3S$
3c	Cl	4-Cl	H	C_2H_5	95	80	$C_{21}H_{20}Cl_2N_4O_3S$
3d	Cl	4-CH_3	H	C_2H_5	176	70	$C_{22}H_{23}ClN_4O_3S$
3e	Cl	H	CH_3	C_2H_5	35	67	$C_{22}H_{23}ClN_4O_3S$
3f	Cl	3-Cl	CH_3	C_2H_5	33	72	$C_{22}H_{22}Cl_2N_4O_3S$
3g	Cl	2-CH_3	H	C_6H_5	135	85	$C_{26}H_{23}ClN_4O_3S$
3h	Cl	2-Cl	H	C_6H_5	40	82	$C_{25}H_{20}Cl_2N_4O_3S$
3i	Cl	4-Cl	CH_3	C_6H_5	35	87	$C_{26}H_{22}Cl_2N_4O_3S$
3j	CH_3O	2-CH_3	H	C_2H_5	123	67	$C_{23}H_{26}N_4O_4S$
3k	CH_3O	2-Cl	H	C_2H_5	27	65	$C_{22}H_{23}ClN_4O_4S$
3l	CH_3O	4-CH_3	H	C_2H_5	167	72	$C_{23}H_{26}N_4O_4S$
3m	CH_3O	H	CH_3	C_2H_5	46	68	$C_{23}H_{26}N_4O_4S$
3n	CH_3O	2-CH_3	H	C_6H_5	134	72	$C_{27}H_{26}N_4O_4S$
3o	CH_3O	2-Cl	H	C_6H_5	82	63	$C_{26}H_{23}ClN_4O_4S$
3p	CH_3O	3-Cl	CH_3	C_2H_5	86	75	$C_{23}H_{25}ClN_4O_4S$
3q	CH_3O	4-Cl	CH_3	C_6H_5	148	80	$C_{27}H_{25}ClN_4O_4S$

3.2. Biological assays

All compounds were submitted to a general preliminary screening including the laboratory tests for algae, lemna, cell suspension, shoot and screening (in the greenhouse trials) for herbicidal activity.

3.2.1. Algae test

The algae test is carried out with *Scenedesmus acutus* in an autotroph Shakeculture, kept at 22 °C and under continuous light. Algae growth is determined quantitatively by means of a Coulter Counter for 24 h after compound application. The initial compound concentration is 10^{-4} M. If, the growth inhibition is greater than 50%, further tests at lower compound concentrations (10^{-5}–10^{-6} M.) are to be performed.

3.2.2. Cell suspension test

Two milliliter samples of cell suspension cultures are placed in sterile test tubes. Defined quantities of the compounds are dissolved in acetone and added to the suspensions. After an incubation period of 8 days the conductivity of the culture medium is determined as a growth parameter. The effect of a compound is expressed as growth inhibition in percent with reference to the control, with zero (0) indicating no growth inhibition and 100, the total growth inhibition.

3.2.3. Lemna test

The lemna test is carried out with *Lemna paucicostata*. The plants are cultured under sterile, autotrophic conditions and continuous light.

The test compounds are added with the inorganic nutrients at an initial concentration of 10^{-4} M. Eight days after application the lemna growth is determined with an image analysing apparatus. (When growth inhibition is greater than 50% further tests at lower compounds concentrations are generally performed.)

3.2.4. Shoot test with Sinapis alba

Two leaf stage shoots, detached from mustard seedlings, are placed upright in plastic vials each of which initially containing 10^{-4} M of the test compound in distilled water. After 3 days, changes in the shoot fresh weight are determined.

3.2.5. Screening for herbicidal activity

A suitable spectrum of mono- and dicotyledonous plants is reared in the greenhouse and treated with the compounds, either pre-emergence or post-emergence.

The normal application rate is equivalent to 3 kg/ha.

The damage caused to the test plants is recorded as a percentage, where 0 represents no damage and 100, total damage.

4. Results and discussion

The reaction of 2-chloro-*N*-(5-substituted-2,3-dihydro-3-benzofuryl)acetamides (**1**) with 3-(aryloxyalkyl)-4-ethyl/phenyl-5-mercapto-1,2,4-triazoles (**2**), resulted in 3-[5-(substitutedphenoxalkyl)-4-ethyl/phenyl-1,2,4-triazole-3-yl)thioacetylamino]-5-substituted-2,3-dihydrobenzofurane (**3a**–**q**). The structure of those compounds was confirmed by IR, ^{1}H NMR and mass spectral data.

IR data were very informative. The amid carbonyl bonds which are common in all compounds are observed at about 1670–1645 cm^{-1}. In the NMR spectra H_A, H_M and H_X protons of 2,3-dihydro-benzofuran resonate according to the AMX system. These protons obtained at about 4.2–4.3 ppm as quartet, 4.5–4.7 ppm as triplet and 5.4–5.6 ppm as multiplet, respectively.

All compounds were inactive for herbicidal activity.

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