Awatef A. Farag, Mohamed F. El Shehry, Samir Y. Abbas*, Safaa N. Abd-Alrahman, Abeer A. Atrees, Hiaat Z. Al-basheer and Yousry A. Ammar

Synthesis of pyrazoles containing benzofuran and trifluoromethyl moieties as possible anti-inflammatory and analgesic agents

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Abstract: Searching for new anti-inflammatory and analgesic agents, we have prepared a series of novel pyrazoles containing benzofuran and trifluoromethyl moieties. The pyrazole derivatives have been synthesized *via* two routes starting from 5-(3-(trifluoromethyl)phenyl azo) salicylaldehyde. The first route involved the synthesis of 2-acetylbenzofuran and then treatment with aldehydes to afford the corresponding chalcones. The cyclization of the latter chalcones with hydrazine hydrate led to the formation of new pyrazoline derivatives. The second route involved the synthesis of benzofuran-2-carbohydrazide and then treatment with formylpyrazoles, chalcones and ketene dithioacetal derivatives to afford the corresponding pyrazole derivatives. Some of the synthesized compounds exhibited anti-inflammatory and analgesic activities.

Keywords: analgesic agents; anti-inflammatory; benzofuran; pyrazoles; trifluoromethyl.

1 Introduction

Analgesic and anti-inflammatory drugs are used in many diseases for relief of pain and inflammation. Most analgesic and anti-inflammatory drugs present a wide range of problems such as efficacy and undesired effects including gastrointestinal tract (GIT) disorders and other unwanted effects. This situation highlights the need for novel, safe and effective analgesic and anti-inflammatory compounds [1–3].

Since the first pyrazolin-5-one was prepared by Knorr [4] in 1883, many papers have reported on the anti-inflammatory, analgesic and antipyretic evaluation of several pyrazoles, pyrazolin-3-ones and pyrazolidine-3,5-diones [5–9]. Many of these derivatives such as phenylbutazone, febrazone, feclobuzone, mefobutazone, suxibuzone and ramifenazone have found their clinical application as nonsteroidal anti-inflammatory drugs (NSAIDs) [10].

The benzofuran derivatives have attracted due to their biological activities and potential application as pharmacological agents [11]. Additionally, various benzofuran derivatives possess anti-inflammatory [12], antidepressant [13], anti-oxidant [14], anticonvulsant [15] and analgesic activity [16].

In addition, many investigations have indicated that the introduction of a trifluoromethyl group in bioactive compounds often improves their pharmacodynamic and pharmacokinetic properties. The CF_3 group has significant effects on the binding affinity in drug–receptor complexes and it can increase membrane permeability and stability against metabolic oxidation [17].

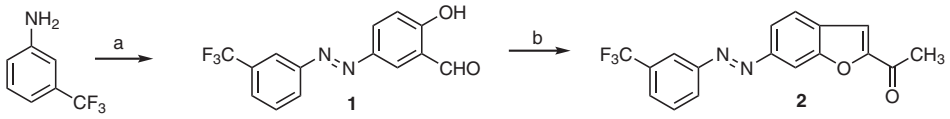
Encouraged by the above facts and in continuation of our interest in the synthesis of bioactive heterocyclic compounds [18–22], we anticipated that the introduction of the important benzofuran moiety and the CF_3 group to a pyrazole nucleus might generate a new group of biologically active compounds that may be potent, selective and less toxic analgesic and anti-inflammatory agents.

2 Results and discussion

2.1 Chemistry

Initially, the core compound 2-acetylbenzofuran derivative **2** was obtained by coupling 3-(trifluoromethyl)

***Corresponding author: Samir Y. Abbas,** Organometallic and Organometalloid Chemistry Department, National Research Centre, Cairo 12622, Egypt, Tel.: +20-233335929, Fax: +20-233370931, E-mail: samiryoussef98@yahoo.com
Awatef A. Farag: Faculty of Science, Chemistry Department, Al-Azhar University (Girls), Cairo, Egypt
Mohamed F. El Shehry: Pesticide Chemistry Department, National Research Centre, Cairo 12622, Egypt
Safaa N. Abd-Alrahman, Abeer A. Atrees and Hiaat Z. Al-basheer: Faculty of Education, Chemistry Department, Taif University, Taif, Saudi Arabia
Yousry A. Ammar: Faculty of Science, Department of Chemistry, Al-Azhar University, Cairo, Egypt

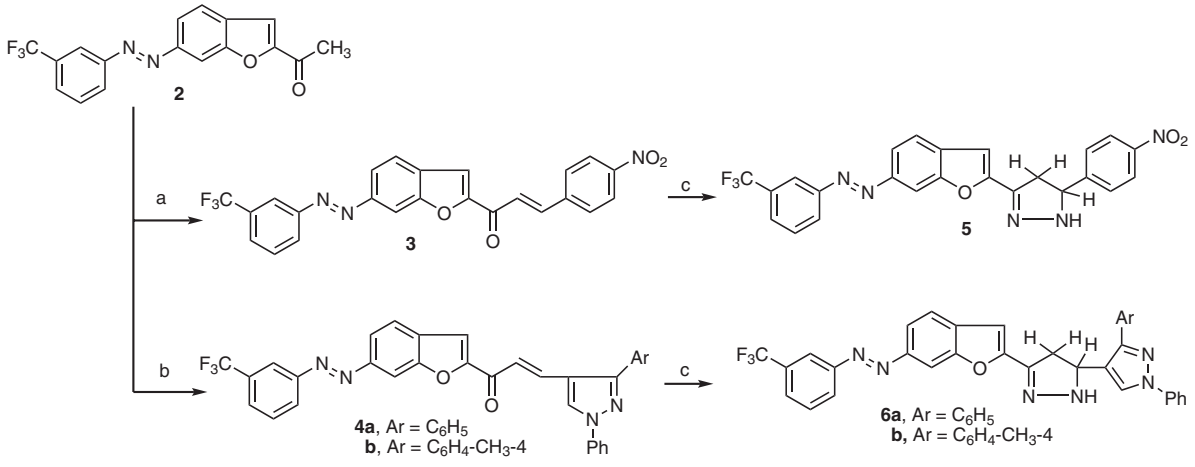


Scheme 1: Synthetic route for acetylbenzofuran **2**: (a) i. HCl, ii. $NaNO_2$, iii. salicylaldehyde, NaOH, stirring, 0 °C; (b) chloroacetone, acetone, K_2CO_3, reflux, 2 h.

benzenediazonium chloride with salicyaldehyde to afford 5-((3-(trifluoromethyl)phenyl)diazenyl)salicylaldehyde (**1**) which was subsequently used for cyclocondensation with chloroacetone in acetone and in the presence of anhydrous potassium carbonate (Scheme 1).

The presence of the acetyl group in compound **2** makes it versatile precursor for the synthesis of chalcones and pyrazoline derivatives. Thus, the Claisen–Schmidt condensation of 2-acetylbenzofuran (**2**) with *p*-nitrobenzaldehyde in ethanolic sodium hydroxide furnished the chalcone derivative **3**. Similarly, condensation of compound **2** with formylpyrazoles afforded the corresponding chalcone derivatives **4a**, **b**. The structures of the latter products were derived from their spectroscopic as well as elemental analytical data. For example, the IR spectrum of compound **3** showed the characteristic band for conjugated C=O at 1664 cm^{-1} and its ^1H NMR spectrum displayed a pair of doublets at δ = 8.36 and 8.49 ppm, with a coupling constant indicating *trans*-olefinic protons. The mass spectrum revealed a molecular ion peak at m/z = 465 (21 %) corresponding to a molecular formula $C_{24}H_{14}F_3N_3O_4$. Cyclocondensation of chalcones **3** and **4a**, **b** with hydrazine hydrate in boiling ethanol furnished the respective pyrazolines **5** and **6a**, **b** (Scheme 2). The structures of the pyrazolines were derived from spectral data and elemental analyses. IR spectra showed the disappearance of the C=O band of chalcones. A strong band appeared at 1590–1602 cm^{-1} and was assigned to C=N of the pyrazoline ring. Pyrazolines **5** and **6a**, **b** showed an additional sharp band in the region 3300–3353 cm^{-1} due to their NH stretching vibration. In the ^1H NMR spectra of pyrazolines **5** and **6a**, **b**, the protons attached to the C-4 and C-5 carbon atoms of the five-membered ring gave an ABX spin system. Chemical shifts and the coupling constant values (*cf*. Experimental section) unequivocally prove the pyrazoline structures. Their ^1H NMR spectra revealed the signals of CH_2 protons of the pyrazoline ring in the region 2.39–3.13 and 4.02–4.14 ppm as a pair of doublets. The CH proton appeared as doublet of doublets at δ = 5.09–5.51 ppm.

The hydrazide and hydrazones derivatives have proved to be good building blocks for the construction of many biological active heterocyclic compounds. When salicylaldehyde derivative **1** was reacted with ethyl bromoacetate in acetone and in the presence of anhydrous potassium carbonate at room temperature, the formyl derivative **7** was obtained rather than the expected ethyl 5-(2-(3-(trifluoromethyl)phenyl)diazenyl)benzofuran-2-carboxylate (**8**) which was obtained in good yield upon heating of **1** with ethyl bromoacetate in acetone under a reflux condition. Benzofuran-2-carbohydrazide **9** was prepared by the



Scheme 2: Synthesis of the chalcone and pyrazole derivatives: (a) 4-nitrobenzaldehyde, EtOH, NaOH aq. r. t., 2 h; (b) formylpyrazoles, EtOH, NaOH aq. r. t., 2 h; (c) hydrazine hydrate, EtOH, reflux, 4 h.

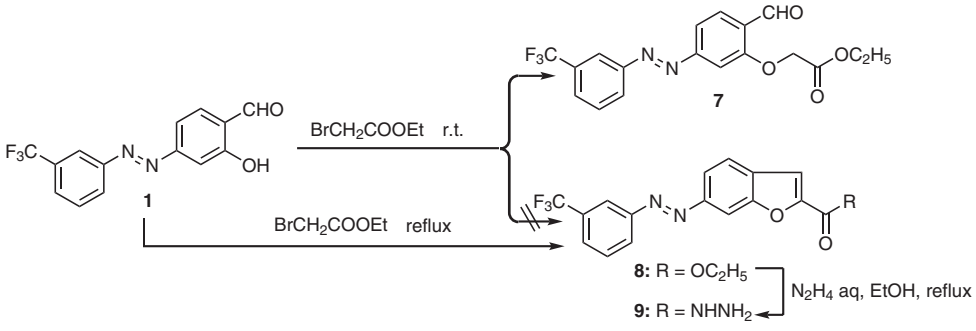
reaction of the ester derivative **8** with hydrazine hydrate in boiling ethanol (Scheme 3). Elemental analyses and spectral data supported the proposed structures.

Condensation of the hydrazide **9** with formylpyrazoles in ethanol under reflux afforded the respective hydrazone derivatives **10a–c**. Also pyrazoline derivatives **11a–c** were prepared through the reaction of hydrazide derivative **9** with some chalcone derivatives. According to previous work [23–27], which was supported by X-ray structure determinations, the suggested reaction mechanism of the cyclization of chalcones with hydrazides or substituted hydrazines to form pyrazolines involves first the condensation of the free amino group of hydrazide with the carbonyl group of the chalcone and then the attachment of the NH group of the hydrazide to the olefinic bond of the chalcone. In our case, this would lead to the Ar group to be attached to C-3 of pyrazoline and the Ar′ group to C-5 of pyrazoline. Finally, the reaction of hydrazide **9** with ketene dithioacetal derivatives in acetic acid under reflux gave only a sole product, which was identified as the pyrazole derivatives **12a**, **b** (Scheme 4). The structures of products were deduced from elemental analysis and spectroscopic data.

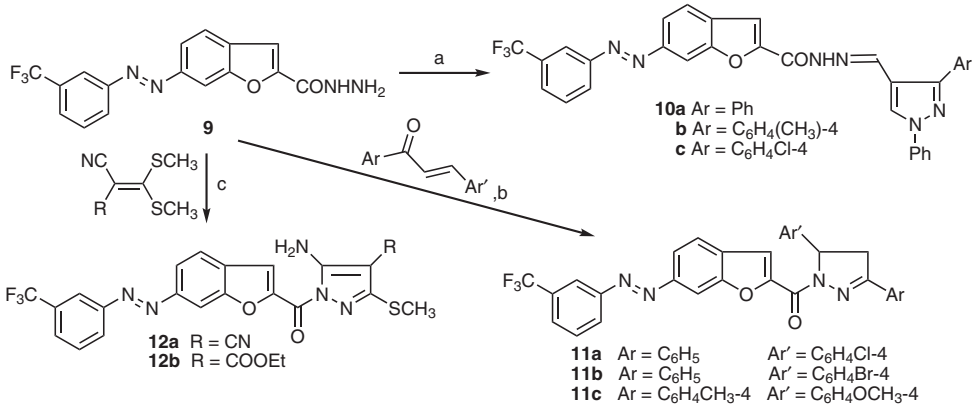
3 Biological activities

3.1 Anti-inflammatory activity

The paw edema test has been widely employed to assay anti-inflammatory agents. It works by measuring the ability of the tested samples in reducing edema induced upon irritant carrageenan. In order to determine the anti-inflammatory activity in acute-phase inflammation in vivo, 11 newly synthesized compounds **4a**, **4b**, **5**, **6a**, **10a**, **10c**, **11a–c** and **12a**, **b** were selected and evaluated with a carrageenan-induced mouse paw edema bioassay in rats [28] using indomethacin as a reference standard. Results were expressed as mean ± SE. The difference between vehicle control and treatment groups was tested using one-way ANOVA followed by the least significant



Scheme 3: Synthetic route for the benzofuran-2-carbohydrazide **9**.



Scheme 4: Synthesis of the different pyrazole derivatives: (a) pyrazole carbaldehyde, EtOH, reflux, 3 h; (b) AcOH, reflux, 3 h; (c) AcOH, reflux, 4 h.

difference. Methods of statistical analysis were performed according to Armitage et al. [29].

According to Table 1, administration of many of the tested compounds 60 min prior to carrageenan injection at a dose of 10 mg kg^{-1} wt caused significant inhibition of paw edema response. Compounds **4b**, **6a** and **12b** caused a significant decrease in paw edema after 2, 3 and 4 h of drug administration, while **11c** and **12a** gave their response after 2 h of administration and continued to the third hour. Compound **10c** showed the effect only after 2 h, but compound **5** significantly decreased the paw edema after 4 h of administration. On the other hand, compounds **5**, **10a** and **11a**, **b** were inactive toward carrageenan-induced edema in comparison to the standard reference indomethacin which markedly and significantly inhibited the paw edema after 2, 3 and 4 h of carrageenan injection. Thus, compounds **4a**, **4b**, **6a**, **10c**, **11c** and **12a**, **b** have good anti-inflammatory activity and compound **4b** was the most potent derivative. Administration (i.p.) of **4b** significantly attenuated edema formation and the inhibitory effect was nearly equipotent to indomethacin. This result suggested that **4b** could be a potential anti-inflammatory agent.

3.1.1 Analgesic activity

The analgesic activity of the above-mentioned 11 derivatives was also evaluated by applying the hot plate test [30] using indomethacin as a standard reference. Results were expressed as mean ± SE. The difference between vehicle control and treatment groups was tested using one-way ANOVA followed by the least significant difference. Methods of statistical analysis were performed according to Armitage et al. [29].

The results reported in Table 1 revealed that compounds **4b**, **6a**, **12a** and **12b** showed significant analgesic activity higher than that obtained by indomethacin. Compounds **4a** and **11a** exhibited an equipotent analgesic effect to or slightly less than indomethacin. Compounds **10c** and **11b** exhibited significant analgesic activity higher than or slightly equipotent to indomethacin only after 2 h of administration. Compound **11c** exhibited the analgesic effect after 1 h of administration only. Compound **5** has no analgesic activity in comparison to the base line of the same group 1 and 2 h post-administration. Thus, it can be concluded that compounds **4a**, **4b**, **6a**, **10a**, **10c**, **11a**, **11b**, **11c**, **12a** and **12b** have significant analgesic activity and compound **12b** is the most potent one.

4 Conclusion

The present work aims to couple benzofuran with a series of functionalized pyrazole derivatives to achieve the synergistic effect. The studies showed that most of the synthesized pyrazole derivatives can be successfully applied in attaining the goal of the desired anti-inflammatory activity. The coupling of benzofuran with pyrazoles and trifluoromethyl group gives an opportunity in medicinal chemistry to improve the clinical and therapeutic effectiveness of a drug that has some undesirable properties hindering its clinical usefulness.

Table 1: Anti-inflammatory and analgesic activities of the tested compounds assessed in comparison to indomethacin.

Compound no.	Anti-inflammatory activity (% inhibition)				Analgesic activity (reaction time in s)	
	1 h	2 h	3 h	4 h	1 h	2 h
Control	–	–	–	–	12.3 ± 0.83	12.2 ± 1.18
4a	12.3 ± 2.5	6.4 ± 6.1	16.8 ± 3.7	22.8 ± 2.3	16.9 ± 1.52	17.0 ± 1.25
4b	3.5 ± 9.8	31.9 ± 7.5	44.3 ± 10.6	41.3 ± 7.1	20.5 ± 2.47	17.8 ± 0.69
5	7.2 ± 4.6	7.4 ± 9.5	11.6 ± 6.4	0.8 ± 5.3	14.1 ± 0.75	12.1 ± 0.85
6a	5.2 ± 7.2	30.8 ± 8.7	33.6 ± 6.7	24.7 ± 6.1	20.1 ± 1.59	20.9 ± 1.54
10a	6.9 ± 7.1	13.8 ± 6.9	15.8 ± 2.1	14.2 ± 7.2	23.9 ± 1.65	18.1 ± 2.64
10c	8.2 ± 3.1	21.3 ± 7.4	12.1 ± 7.1	2.1 ± 2.2	14.8 ± 1.02	21.2 ± 1.19
11a	7.8 ± 3.7	18.1 ± 6.8	17.6 ± 8.0	0.7 ± 5.3	16.7 ± 1.66	17.9 ± 1.23
11b	6.3 ± 6.2	5.1 ± 5.1	6.1 ± 02	15.5 ± 5.5	14.5 ± 0.93	18.5 ± 1.47
11c	22.8 ± 5.1	37.2 ± 4.6	22.3 ± 3.3	10.8 ± 3.1	17.1 ± 1.89	9.33 ± 0.89
12a	14.0 ± 7.2	23.4 ± 6.6	24.5 ± 4.7	10.7 ± 5.2	18.8 ± 1.46	19.2 ± 1.00
12b	9.9 ± 6.5	29.8 ± 5.8	31.6 ± 7.0	21.7 ± 7.4	25.3 ± 1.38	19.1 ± 0.61
Indomethacin	14.8 ± 5.3	55.3 ± 5.1	54.4 ± 4.5	49.2 ± 5.7	17.9 ± 0.32	18.0 ± 0.28

5 Experimental section

All melting points were determined on an electrothermal Gallenkamp apparatus (Weiss-Gallenkamp, London, UK) and are uncorrected. The IR spectra were measured on a Mattson 5000 FTIR spectrometer (SVC, CA, USA) in potassium bromide disks. The NMR spectra were recorded in [D_6] DMSO on a Bruker WP spectrometer (500 MHz) (The Bruker Corporation) and the chemical shifts (δ values) were reported in ppm downfield from trimethylsilyl (TMS) as an internal standard. The mass spectra were recorded on a Finnigan MAT 212 instrument (Bremen, Germany), with the ionizing voltage of 70 eV, at Faculty of Science, Cairo University. Elemental analyses were carried out by the Microanalytical Unit of the Faculty of Science, Cairo University. All fine chemicals were purchased from Merck, Germany.

5.1 Preparation of 2-hydroxy-5-((3-(trifluoromethyl)phenyl)diazenyl) benzaldehyde (1)

An aqueous solution of $NaNO_2$ (0.69 g, 0.01 mol) was slowly added to a solution of 3-trifluoromethylaniline (1.61 g, 0.01 mol) in a mixture of concentrated hydrochloric acid (16 mL) and water (16 mL) with stirring and settled for about 20 min in an ice bath at 0 °C. Salicylaldehyde solution (1.22 g, 0.01 mol), NaOH (5 g) and distilled water (100 mL) were added slowly to the resulting solution with stirring; the resulting mixture reacted for 4 h at 0 °C. The reaction mixture was acidified by HCl. The solid product obtained was collected by filtration and crystallized from cyclohexane to give the corresponding salicylaldehyde derivative **1** as orange crystals. Yield: 84 %; m.p.: 132–134 °C. – IR: ν = 3446 (OH), 1649 (C=O) cm^{-1}. – ^{1}H NMR (500.14 MHz, [D_6]DMSO, 25 °C, TMS): δ = 7.14 (d, 1H, J = 9.24 Hz, Ar-H), 7.50 (m, 1H, Ar-H), 7.67 (d, 1H, J = 6.9 Hz, Ar-H), 7.83 (d, 1H, J = 6.9 Hz, Ar-H), 7.90 (s, 1H, Ar-H), 8.05 (d, 1H, J = 9.24 Hz, Ar-H), 8.14 (s, 1H, Ar-H), 10.32 (s, 1H, CHO), 11.73 (br, 1H, OH). – $C_{14}H_9F_3N_2O_2$ (294.23): calcd. C 57.15, H 3.08, N 9.52; found C 57.32, H 3.13, N 9.61.

5.2 1-(6-((3-(Trifluoromethyl)phenyl) diazenyl)benzofuran-2-yl)ethanone (2)

To a solution of salicyaldehyde derivative **1** (2.94 g, 0.01 mol) in acetone (40 mL), chloroacetone (0.93 g, 0.01 mol) and K_2CO_3 (2.0 g) were added. The solution was heated under reflux for 2 h, cooled to room temperature and suspended in ice-cooled water. The solid product obtained was collected by filtration and crystallized from ethanol to give **2**. Yield: 74 %; m.p.: 79–81 °C. – IR: ν = 1689 (C=O) cm^{-1}. – ^{1}H NMR (500.14 MHz, [D_6]DMSO, 25 °C, TMS): δ = 2.52 (s, 3H, CH_3), 6.68–8.18 (m, 8H, Ar-H). – $C_{17}H_{11}F_3N_2O_2$ (332.28): calcd. C 61.45, H 3.34, N 8.43; found C 61.54, H, 3.48, N 8.54.

5.3 General method for the preparation of chalcone derivatives 3 and 4a,b

2-Acetylbenzofuran **2** (3.32 g, 0.01 mol) and the selected aldehydes (0.01 mol) were taken in ethanol (25 mL) and cooled. Ten percent aqueous sodium hydroxide solution (2.5 mL) was added to the above solution with constant stirring, until the turbidity appears. The reaction mixture was further stirred for 2 h and left overnight. The mixture was carefully acidified using dilute hydrochloric acid to obtain deep colored (yellow-orange) solid. The product obtained was filtered, washed with water and recrystallized from ethanol.

5.3.1 3-(4-Nitrophenyl)-1-(6-((3-(trifluoromethyl)phenyl) diazenyl)benzofuran-2-yl)prop-2-en-1-one (3)

Yield: 82 %; m.p.: 227–229 °C. – IR: ν = 1644 (C=O) cm^{-1}. – ^{1}H NMR (500.14 MHz, [D_6]DMSO, 25 °C, TMS): δ = 7.73–8.31 (m, 12 H, Ar-H), 8.36 (d, 1H, J = 13.1 Hz, olefinic CH), 8.49 (d, 1H, J = 12.8 Hz, olefinic CH). – ^{13}C NMR (125.76 MHz, [D_6]DMSO): δ = 113.8, 116.6, 118.8, 120.6, 123.1 (2C), 124.4 (3C), 126.2, 126.9, 127.1, 128.2, 130.4 (3C), 131.3 (2C), 141.2, 141.5, 148.9, 149.4, 152.6, 154.9. – MS (EI, 70 eV): m/z (%) = 465 (21.4) $[M]^+$, 320 (7.2), 292 (100) 262 (14.8), 205 (11.3), 179 (8.1), 160 (7.0) 145 (67.8), 130 (15.5), 118 (7.8), 102 (27.5), 89 (22.0), 75 (13.3). – $C_{24}H_{14}F_3N_3O_4$ (465.38): calcd. C 61.94, H 3.03, N 9.03; found C 61.82, H 3.23, N 9.13.

5.3.2 3-(1,3-Diphenyl-1H-pyrazol-4-yl)-1-(6-((3-(trifluoromethyl)phenyl)diazenyl)benzofuran-2-yl) prop-2-en-1-one (4a)

Yield: 78 %; m.p.: 224–226 °C. – IR: ν = 1640 (C=O) cm^{-1}. – ^{1}H NMR (500.14 MHz, [D_6]DMSO, 25 °C, TMS): δ = 6.68–8.11 (m, 19 H, Ar-H), 8.49 (d, 1H, J = 16.1 Hz, olefinic CH), 9.34 (d, 1H, J = 15.8 Hz, olefinic CH). – $C_{33}H_{21}F_3N_4O_2$ (562.54): calcd. C 70.46, H 3.76, N 9.96; found C 70.48, H 3.83, N 9.74.

5.3.3 3-(1-Phenyl-3-p-tolyl-1H-pyrazol-4-yl)-1-(6-((3-(trifluoromethyl)phenyl)diazenyl) benzofuran-2-yl) prop-2-en-1-one (4b)

Yield: 77 %; m.p.: 215–217 °C. – IR: ν = 1643 (C=O) cm^{-1}. – ^{1}H NMR (500.14 MHz, [D_6]DMSO, 25 °C, TMS): δ = 2.51 (s, 3H, CH_3), 7.41–8.20 (m, 18H, Ar-H), 8.49 (d, 1H, J = 15.3 Hz,

olefinic CH), 9.34 (d, 1H, J = 15.1 Hz, olefinic CH). – $C_{34}H_{23}F_3N_4O_2$ (576.57): calcd. C 70.83, H 4.02, N 9.72; found C 70.71, H 4.16, N 9.53.

5.4 General method for the preparation of 4,5-dihydropyrazole derivatives 5, 6a, b

To a solution of the propenone **3** or **4a**, **b** (0.01 mol) in ethanol (60 mL), hydrazine hydrate (0.6 g, 0.012 mol) was added. The reaction mixture was heated under reflux for 4 h. After cooling the separated solid was filtered and recrystallized from ethanol.

5.4.1 5-(4-Nitrophenyl)-3-(6-((3-(trifluoromethyl)phenyl) diazenyl)benzofuran-2-yl)-4,5-dihydro-1H-pyrazole (5)

Yield: 78 %; m.p.: 212–214 °C. – IR: ν = 3353 (NH), 1590 (C=N) cm^{-1}. – ^1H NMR (500.14 MHz, [D_6]DMSO, 25 °C, TMS): δ = 3.13 (dd, 1H, J = 16.50 and 9.86 Hz, H_A of pyrazoline), 4.02 (dd, 1H, J = 16.50 and 7.32 Hz, H_B of pyrazoline), 5.51 (dd, 1H, J = 9.85 and 7.40 Hz, H_X of pyrazoline), 6.86–8.51 (m, 19 H, Ar-H + NH pyrazoline). – $C_{24}H_{16}F_3N_5O_3$ (479.41): calcd. C 60.13, H 3.36, N 14.61; found C 60.22, H 3.16, N 14.53.

5.4.2 1,3-Diphenyl-4-(3-(6-((3-(trifluoromethyl)phenyl) diazenyl)benzofuran-2-yl)-4,5-di-hydro-1H-pyrazol-5-yl)-1H-pyrazole (6a)

Yield: 76 %; m.p.: 219–221 °C. – IR: ν = 3312 (NH) cm^{-1}. – ^1H NMR (500.14 MHz, [D_6]DMSO, 25 °C, TMS): δ = 3.07 (dd, 1H, J = 16.43 and 9.76 Hz, H_A of pyrazoline), 4.14 (dd, 1H, J = 16.31 and 7.11 Hz, H_B of pyrazoline), 5.09 (dd, 1H, J = 9.71 and 7.22 Hz, H_X of pyrazoline), 6.86–8.51 (m, 20 H, Ar-H + NH pyrazoline). – MS (EI, 70 eV): m/z (%) = 576 (44.2) $[M]^+$, 577 (13.1) [M+1], 575 (38.9) [M–1], 573 (29.6), 548 (13.5), 402 (20.6), 401 (48.3), 245 (31.5), 201 (18.4) 145 (52.0), 104 (30.8), 77 (100), 76 (14.6), 75 (19.9). – $C_{33}H_{23}F_3N_6O$ (576.57): calcd. C 68.74, H 4.02, N 14.58; found C 68.87, H 4.22, N 14.64.

5.4.3 1-Phenyl-3-p-tolyl-4-(3-(6-((3-(trifluoromethyl) phenyl)diazenyl)benzofuran-2-yl)-4,5-dihydro-1H-pyrazol-5-yl)-1H-pyrazole (6b)

Yield: 74 %; m.p.: 196–198 °C. – IR: ν = 3300 (NH), 3059 (CH-aryl), 1602 (C=N) cm^{-1}. – ^1H NMR (500.14 MHz, [D_6]DMSO, 25 °C, TMS): δ = 2.39 (s, 3H, CH_3), 3.13 (dd, 1H, J = 16.41 and 9.74 Hz, H_A of pyrazoline), 4.14 (dd, 1H, J = 16.32 and 7.32 Hz, H_B of pyrazoline), 5.15 (dd, 1H, J = 9.78 and 7.35 Hz, H_X of pyrazoline), 6.86–8.51 (m, 19H, Ar-H + NH pyrazoline). – $C_{34}H_{25}F_3N_6O$ (590.6): calcd. C 69.14, H 4.27, N 14.23; found C 69.01, H 4.18, N 14.29.

5.5 Ethyl 2-(2-formyl-5-((3-(trifluoromethyl) phenyl)diazenyl)phenoxy)acetate (7)

To a solution of salicyaldehyde derivative **1** (2.94 g, 0.01 mol) in acetone (40 mL), ethyl bromomacetate (1.67 g, 0.01 mol) and K_2CO_3 (2 g) were added. The solution was stirred at room temperature for 3 h, cooled to room temperature and suspended with ice-cooled water. The solid product obtained was collected by filtration and crystallized from THF to give **7**. Yield: 74 %; m.p.: 84–86 °C. – IR: ν = 1746, 1692 (C=O) cm^{-1}. – ^1H NMR (500.14 MHz, [D_6] DMSO, 25 °C, TMS): δ = 1.23 (t, 3H, J = 6.98 Hz, CH_3-ester), 4.23 (q, 2H, J = 7.01 Hz, CH_2-ester), 5.14 (s, 2H, CH_2), 7.45 (d, 2H, J = 7.50 Hz, Ar-H); 7.82–7.94 (m, 2H, ArH), 8.15–8.26 (m, 3H, ArH), 10.48 (s, 1H, CHO). – ^{13}C NMR (125.76 MHz, [D_6] DMSO): δ = 14.3 (CH_3-ester), 61.4 (CH_2), 66.5 (CH_2), 115.6, 118.9, 122.3, 126.9, 130.8, 131.2, 146.5, 152.5, 162.8, 168.8 (C=O), 189.1 (CHO). – $C_{18}H_{15}F_3N_2O_4$ (380.32): calcd. C 56.85, H 3.98, N 7.37; found C 56.85, H 3.98, N 7.37.

5.6 Ethyl 6-((3-(trifluoromethyl)phenyl) diazenyl)benzofuran-2-carboxylate (8)

To a solution of salicyaldehyde derivative **1** (2.94 g, 0.01 mol) in acetone (40 mL), ethyl bromomacetate (1.67 g, 0.01 mol) and K_2CO_4 (2 g) were added. The solution was heated under reflux for 3 h, cooled to room temperature and suspended with ice-cooled water. The solid product obtained was collected by filtration and crystallized from THF to give the carboxylate derivative **8** as colorless crystals. Yield: 79 %; m.p.: 194–196 °C. – IR: ν = 1732 (C=O) cm^{-1}. – ^1H NMR (500.14 MHz, [D_6]DMSO, 25 °C, TMS): δ = 1.21 (t, 3H, J = 6.98 Hz, CH_3-ester), 4.19 (q, 2H, J = 7.01 Hz, CH_2-ester), 7.44–7.98 (m, 6H, ArH), 8.15–8.26 (m, 4H, ArH). – $C_{18}H_{13}F_3N_2O_3$ (362.30): calcd. C 59.67, H 3.62, N 7.73; found C 59.67, H 3.62, N 7.73.

5.7 6-((3-(Trifluoromethyl)phenyl)diazenyl) benzofuran-2-carbohydrazide (9)

A solution of benzofuran-2-carboxylate **8** (3.62 g, 0.01 mol) in ethanol (20 mL) was treated with hydrazine hydrate (0.6 g, 0.012 mol). The mixture was heated under reflux for 3 h. The solid product obtained was collected by filtration

and crystallized from dioxane to give the corresponding hydrazide derivative **9**. Yield: 74 %; m.p.: 204–206 °C. – IR: ν = 3425, 3216 (NH_2, NH), 3073 (CH-aryl), 1684 (C=O), 1608 (C=N), 1588 (N=N) cm^{-1}. – ^1H NMR (500.14 MHz, [D_6]DMSO, 25 °C, TMS): δ = 2.63 (br, 2H, NH_2); 6.24–7.72 (m, 8H, Ar-H), 8.85 (s, 1H, NH). – MS (EI, 70 eV): m/z (%) = 348 (8.6) $[M]^+$, 291 (20.7), 175 (13.6), 161 (59.3), 145 (100), 133 (15.0), 126 (18.6), 118 (38.6), 105 (10.7), 89 (47.9), 76 (25.0). – $C_{16}H_{11}F_3N_4O_2$ (348.28): calcd. C 55.18, H 3.18, N 16.09; found C 55.21, H 3.34, N 16.19.

5.8 General procedure for the condensation of the hydrazide 9 with formylpyrazole

To a solution of the hydrazide **9** (3.48 g, 0.01 mol), in dioxane (30 mL), formylpyrazole (0.01 mol) was added and the reaction mixture was heated under reflux for 3 h. The solid obtained upon cooling was collected by filtration, dried and recrystallized from dioxane.

5.8.1 N′-((1,3-Diphenyl-1H-pyrazol-4-yl)methylene)-6-((3-(trifluoromethyl)phenyl)diazenyl)benzofuran-2-carbohydrazide (10a)

Yield: 92 %; m.p.: >300 °C. – IR: ν = 3217 (NH), 3073 (CH-aryl.), 1682 (C=O), 1607 (C=N), 1538 (N=N), 1094 (C–O–C of benzofuran) cm^{-1}. – ^1H NMR (500.14 MHz, [D_6]DMSO, 25 °C, TMS): δ = 6.94–8.72 (m, 20 H, Ar-H), 10.12 (br, 1H, NH). – MS (EI, 70 eV): m/z (%) = 578 (2.1) $[M]^+$, 290 (15.6), 175 (16.3), 145 (100), 135 (12.2), 117 (84.0). 103 (10.1), 90 (50.3), 77 (19.8). – $C_{32}H_{21}F_3N_6O_2$ (578.54): calcd. C 66.43, H 3.66, N 14.53; found C 66.57, H 3.84, N 14.71.

5.8.2 N′-((1-Phenyl-3-p-tolyl-1H-pyrazol-4-yl) methylene)-6-((3-(trifluoromethyl)phenyl) diazenyl)benzofuran-2-carbohydrazide (10b)

Yield: 92 %; m.p.: >300 °C. – IR: ν = 3207 (NH), 1687 (C=O) cm^{-1}. – ^1H NMR (500.14 MHz, [D_6]DMSO, 25 °C, TMS): δ = 2.32 (s, 3H, CH_3), 6.68–8.18 (m, 19H, Ar-H), 10.04 (br, 1H, NH). – $C_{33}H_{23}F_3N_6O_2$ (592.54): calcd. C 66.89, H 3.91, N 14.18; found C 66.94, H 3.76, N 14.23.

5.8.3 N′-((3-(4-Chlorophenyl)-1-phenyl-1H-pyrazol-4-yl)methylene)-6-((3-(trifluoromethyl)phenyl) diazenyl)benzofuran-2-carbohydrazide (10c)

Yield: 92 %; m.p.: >300 °C. – IR: ν = 3221 (NH), 1682 (C=O) cm^{-1}. – ^1H NMR (500.14 MHz, [D_6]DMSO, 25 °C, TMS): δ = 6.87–8.86 (m, 19 H, Ar-H), 10.55 (br, 1H, NH). – $C_{32}H_{20}ClF_3N_6O_2$ (612.13): calcd. C 62.70, H 3.29, N 13.71; found C 62.87, H 3.34, N 13.62.

5.9 General procedure of synthesis of 4,5-dihydro-pyrazole derivatives 11a–c

To a solution of hydrazide **9** (3.48 g, 0.01 mol) in glacial acetic acid (50 mL), substituted chalcones (0.01 mol) were added and the reaction mixture was refluxed for 6 h. The solid obtained upon cooling was collected by filtration, dried and recrystallized from butanol.

5.9.1 (5-(4-Chlorophenyl)-3-phenyl-4,5-dihydro-1H-pyrazol-1-yl)(6-((3-(trifluoromeths- yl)phenyl) diazenyl)benzofuran-2-yl)methanone (11a)

Yield: 92 %; m.p.: >300 °C. – IR: ν = 1682 (C=O) cm^{-1}. – ^1H NMR (500.14 MHz, [D_6]DMSO, 25 °C, TMS): δ = 3.42 (dd, 1H, J = 18.44 and 4.07 Hz, H_A of pyrazoline), 3.86 (dd, 1H, J = 18.21 and 10.17 Hz, H_B of pyrazoline), 5.57 (dd, 1H, J = 10.71 and 4.22 Hz, H_X of pyrazoline), 6.68–7.98 (m, 17H, Ar-H). – MS (EI, 70 eV): m/z (%) = 572 (25) $[M]^+$, 117 (100). – $C_{31}H_{20}ClF_3N_4O_2$ (572.96): calcd. C 64.98, H 3.52, N 9.78; found C 64.98, H 3.52, N 9.78.

5.9.2 (5-(4-Bromophenyl)-3-phenyl-4,5-dihydro-1H-pyrazol-1-yl)(6-((3-(trifluoromethyl)phenyl) diazenyl)benzofuran-2-yl)methanone (11b)

Yield: 92 %; m.p.: >300 °C. – IR: ν = 1682 (C=O) cm^{-1}. – ^1H NMR (500.14 MHz, [D_6]DMSO, 25 °C, TMS): δ = 3.42 (dd, 1H, J = 17.32 and 3.86 Hz, H_A of pyrazoline), 3.86 (dd, 1H, J = 18.32 and 9.32 Hz, H_B of pyrazoline), 5.57 (dd, 1H, J = 10.32 and 3.98 Hz, H_X of pyrazoline), 6.68–7.98 (m, 12H, Ar-H). – MS (EI, 70 eV): m/z (%) = 616 (22.1) $[M]^+$, 329 (34.9), 223 (67.3), 145 (55.6), 121 (100), 77 (69.8). – $C_{31}H_{21}F_3N_4O_3$ (554.52): calcd. C 67.15, H 3.82, N 10.10; found C 67.31, H 3.64, N 10.23.

5.9.3 (5-(4-Methoxyphenyl)-3-p-tolyl-4,5-dihydro-1H-pyrazol-1-yl)(6-((3-(trifluoromethyl)phenyl) diazenyl)benzofuran-2-yl)methanone (11c)

Yield: 92 %; m.p.: >300 °C. – IR: ν = 3217 (NH), 3073 (CH-aryl.), 1682 (C=O), 1607 (C=N), 1538 (N=N), 1094 (C–O–C of benzofuran) cm^{-1}. – ^1H NMR (500.14 MHz, [D_6]DMSO, 25 °C, TMS): δ = 2.59 (s, 3H, CH_3), 3.23 (s, 3H, OCH_3), 3.42

(dd, 1H, J = 18.44 and 4.07 Hz, H_A of pyrazoline), 3.86 (dd, 1H, J = 18.21 and 10.17 Hz, H_B of pyrazoline), 5.57 (dd, 1H, J = 10.71 and 4.22 Hz, H_X of pyrazoline), 6.98–7.98 (m, 16H, Ar-H). – MS (EI, 70 eV): m/z (%) = 582 (2.1) $[M]^+$, 402 (22.1), 290 (14.9), 161 (26.3), 117 (100). – $C_{33}H_{25}F_3N_4O_3$ (582.57): calcd. C 68.04, H 4.33, N 9.62; found C 68.17, H 4.54, N 9.75.

5.10 General procedure of synthesis of ethyl 5-amino-3-(methylthio)-1H-pyrazole derivatives 12a, b

To a solution of hydrazide **9** (3.48 g, 0.01 mol) in glacial acetic acid (50 mL), substituted ketene dithioacetals (0.01 mol) were added and the reaction mixture was refluxed for 4 h. The solid obtained upon cooling was collected by filtration, dried and recrystallized from butanol.

5.10.1 5-Amino-3-(methylthio)-1-(6-((3-(trifluoromethyl) phenyl)diazenyl)benzofuran-2-carbonyl)-1H-pyrazole-4-carbonitrile (12a)

Yield: 92 %; m.p.: >300 °C. – IR: ν = 3217, 3196 (NH_2), 2214 (C≡N), 1694 (C=O) cm^{-1}. – ^1H NMR (500.14 MHz, [D_6]DMSO, 25 °C, TMS): δ = 2.49 (s, 3H, SCH_3), 6.51 (br, 2H, NH_2), 6.68–8.18 (m, 8H, Ar-H). – $C_{21}H_{13}F_3N_6O_2S$ (470.43): calcd. C 53.62, H 2.79, N 17.86; found C 53.47, H 2.74, N 17.75.

5.10.2 Ethyl 5-amino-3-(methylthio)-1-(6-((3-(trifluoromethyl)phenyl)diazenyl)benzofuran-2-carbonyl)-1H-pyrazole-4-carboxylate (12b)

Yield: 92 %; m.p.: >300 °C. – IR: ν = 3206, 3191 (NH_2), 1686 (C=O) cm^{-1}. – ^1H NMR (500.14 MHz, [D_6]DMSO, 25 °C, TMS): δ = 1.29 (t, 3H, J = 6.98 Hz, CH_3-ester), 2.49 (s, 3H, SCH_3), 4.30 (q, 2H, J = 7.01 Hz, CH_2-ester), 6.51 (br, 2H, NH_2), 6.68–8.18 (m, 8H, Ar-H). – $C_{23}H_{18}F_3N_5O_4S$ (517.48): calcd. C 53.38, H 3.51, N 13.53; found C 53.17, H 3.64, N 13.75.

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