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Novel Straight-Chained Sulfanyl Members of Arylamino-1,4-naphthoquinones: Synthesis and Characterization

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Abstract: The aim of this paper is to describe the synthesis and characterization of new members of straight-chained sulfanyl derivatives of arylamino-1,4-naphthoquinones. 2-(4-(trifluoromethyl)phenylamino)-3-chloronaphthalene-1,4-dione (**3a**) and 2-(3-(trifluoromethyl)phenylamino)-3-chloronaphthalene-1,4-dione (**3b**) prepared by a nucleophilic substitution reaction between 2,3-dichloronaphthalene-1,4-dione' (**1**) and arylamines containing a trifluoro group at the meta or para positions (**2a, 2b**) were used as building blocks for straight-chained sulfanyl arylamino-1,4-naphthoquinones. The structures of all the novel compounds (**5a-f**) were established by spectroscopic evidence including FTIR, ^{1}H NMR, ^{13}C NMR, and MS data.

Keywords: Sulfanyl 1,4-naphthoquinone; arylamine; trifluoromethyl group.

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INTRODUCTION

Intense efforts are being made to synthesize good candidates for both further studies of chemical and structural modifications as well as biological applications (1-3). The naphthoquinone moiety, a common element in a number of different natural and synthetic structures such as menadione, lapachol and NQ304 (2-chloro-3-(4-hexylphenyl)-amino-1,4-naphthoquinone), is an important factor in the discovery of active substances. It is understood from the literature that the biological activity may be effected by the number and position of the substituents in the naphthoquinone moiety (4-8). It is no surprise that an impressive number of antibiotics like pyrano naphthoquinones involving eleutherin, nanaomycin, and kalafungin contains a naphthoquinone core (9-11). The biological potential of a derivative of naphthoquinone can be altered by the addition of a substituted aniline to the structure (12, 13). The electron donating or withdrawing features of the substituents on the aniline influence their redox functions (12). As the small and electron withdrawing group, trifluoromethyl (CF_3) has unique chemical properties due to its stereoelectronic and physiological profile that is relevant to the position of -CF_3 on aniline ring (13, 14). In addition to their marked antimicrobial, antifungal, antimalarial, antileishmanial, antiviral, anti-oxidant properties, sulfanyl amino derivatives of 1,4-naphthoquinones have also been found to be effective in inhibiting the proliferation of cancer cells (15-17). There are many reports on anticancer screening of 1,4-naphthoquinones containing an amino, a substituted amino or sulfanyl substituents in the 2-position that proves the biological convenience of this structures (18).
In the frame of our studies on the synthesis of new naphthoquinone derivatives with antimicrobial, antibiofilm, and anticancer activities, we have recently reported the effect of a number of sulfanyl arylamino-1,4-naphthoquinones on Gram positive/negative bacteria and human tumor cell lines (19).

From the previous studies of structural modifications including changes of substituents in the side chain of the naphthoquinone ring, it can be deduced that the presence of an arylamine containing trifluoromethyl group and straight-chained sulfanyl compounds attached to the quinone ring can contribute to improve the bioactivity of these compounds. Thus, it is planned to synthesize and characterize several new straight-chained sulfanyl 1,4-naphthoquinones bearing arylamine rings with trifluoromethyl group so prevalent in drug molecules.

MATERIALS AND METHODS

All chemicals were commercially purchased from various suppliers and were used directly without further purification. The purity of the reaction products was monitored by thin-layer chromatography on analytical thin layer chromatography (TLC), purchased from Merck - KGaA (silica gel 60 F_{254}) based on Merck DC-plates (aluminum based). Visualization of the chromatogram was performed by UV light (254 nm). Column chromatographic separations were carried out using silica gel 60 (Merck, 63–200 μm particle size, 60–230 mesh). NMR spectra were recorded with a Varian UNITY INOVA instrument (500 MHz frequency for ^{1}H and 125 MHz frequency for ^{13}C NMR) with $CDCl_3$ as solvent referring to signal center at δ 7.19 td (triplet of doublet), h (hextet) and δ 76.0 ppm, respectively. The peak multiplicities are abbreviated as follows: s (singlet), br s (broad singlet), d (doublet), t (triplet), p (pentet), dd (doublet of doublets) and m (multiplet). Chemical shifts were given in ppm (δ) relative to TMS, and coupling constants (J) were expressed in hertz (Hz). FTIR spectra were recorded as ATR on an Agilent Cary 630 FT-IR spectrometer. Mass spectra were obtained on a ThermoFinnigan LCQ Advantage MAX MS/MS spectrometer equipped with an ESI (Electrospray ionization) sources. Melting points (mp) were determined with a Buchi B-540 melting point apparatus and were uncorrected.

General Procedure for Synthesis of the Arylamino Chloro 1,4-Naphthoquinone Derivatives (3a-b)

2-Arylamino-3-chloro-1,4-naphthoquinone derivatives (**3a-b**) were prepared from the reaction between '2,3-dichloronaphthalene-1,4-dione (**1**) with trifluoromethyl-substituted arylamines (**2a-b**) according to methods reported in the literature and references cited therein (20-22).

General Procedure for Synthesis of the Straight-chained Sulfanyl Arylamino-1,4-naphthoquinone Derivatives (**5a-f**)

2-Arylamino-3-chloro-1,4-naphthoquinone derivatives (**3a-b**) and straight-chained sulfanyl compounds **(4a, 4b, 4c)** in CH_2Cl_2 were stirred at room temperature by using Et_3N as stated in the literature (2). The resulting solution was extracted with 100 mL chloroform then washed with water (4x100 mL) and dried over calcium chloride. The solvent was removed *in vacuo*. The residue was subjected to column chromatography on silica gel using suitable solvents to give the products.

2-(4-(trifluoromethyl)phenylamino)-3-(propylthio)naphthalene-1,4-dione (**5a**). It was synthesized from 2-(4-(trifluoromethyl)phenylamino)-3-chloronaphthalene-1,4-dione (**3a**) and propane-1-thiol (**4a**) as red oil by using the general procedure. Yield: 0.079 g, 71%. FTIR (ATR) ν(cm^{-1}): 3324 (-NH), 3065 ($CH_{arom.}$), 2921, 2846 ($CH_{aliph.}$), 1681, 1652 (C=O), 1600, 1569 (C=C). ^{1}H NMR (500 MHz, *CDCl₃*) δ (ppm): 8.20-8.17 dd, *J: 7.79, 1.19 Hz*, 1H (-$CH_{arom.}$); 8.14-8.12 dd, *J: 7.53, 1.03 Hz*, 1H (-$CH_{arom.}$); 7.83 br s, 1H (-NH); 7.80-7.76 td, *J: 7.53, 1.47 Hz*, 1H (-$CH_{arom.}$); 7.74-7.70 td, *J: 7.49, 1.42 Hz*, 1H (-$CH_{arom.}$); 7.62-7.60 d, *J: 8.44 Hz*, 2H (-$CH_{arom.}$); 7.09-7.07 d, *J: 8.69 Hz*, 2H (-$CH_{arom.}$); 2.64-2.61 t, *J: 7.39 Hz*, 2H (-SCH_2); 1.47-1.42 m, 2H (-CH_2-); 0.87-0.83 t, *J: 7.31 Hz*, 3H (-CH_3). ^{13}C NMR (125 MHz, *CDCl₃*) δ(ppm): 181.2, 180.1, 143.7, 141.5, 134.6, 133.3, 133.2, 130.6, 127.0, 126.8, 125.8, 121.9, 121.2, 35.7, 22.9, 13.2. MS (ESI+) m/z (%): 391 (100, $[M]^+$). Anal. Calcd. for $C_{20}H_{16}F_3NO_2S$ (391.41).

2-(4-(Trifluoromethyl)phenylamino)-3-(pentylthio)naphthalene-1,4-dione (**5b**). It was synthesized from 2-(4-(trifluoromethyl)phenylamino)-3-chloronaphthalene-1,4-dione (**3a**) and pentane-1-thiol (**4b**) as a red powder by using the general procedure. Yield: 0.046 g, 39%; mp 93-94 °C. FTIR (ATR) ν(cm^{-1}): 3305 (-NH), 3061 ($CH_{arom.}$), 2928, 2846, 2878 ($CH_{aliph.}$), 1669, 1656 (C=O), 1602, 1554 (C=C). ^{1}H NMR (500 MHz, *CDCl₃*) δ (ppm): 8.19-8.15 dd, *J: 7.81, 0.97 Hz*, 1H (-CH_{arom}); 8.13-8.08 d, *J: 7.32, 0.98 Hz*, 1H (-CH_{arom}); 7.82 br s, 1H (-NH); 7.78-7.75 td, *J: 7.32, 1.46 Hz*, 1H (-CH_{arom}); 7.73-7.67 td, *J: 7.81, 1.46 Hz*, 1H (-CH_{arom}); 7.63-7.56 d, *J: 8.29 Hz*, 2H (-CH_{arom}); 7.10-7.02 d, *J: 8.29 Hz*, 2H (-CH_{arom}); 2.56-2.64 t, *J: 7.8 Hz*, 2H (S-CH_2-); 1.34-1.44 m, 2H (-CH_2-); 1.24-1.14 m, 4H (-CH_2); 0.86- 0.76 t, *J: 7.33 Hz*, 3H (-CH_3). ^{13}C NMR (125 MHz, *CDCl₃*) δ(ppm): 181.2, 180.1, 143.4, 141.3, 134.6, 133.3, 133.1, 130.6, 127.0, 126.8, 125.7, 122.0, 121.1, 33.6; 30.7, 29.0, 22.1, 13.8. MS (ESI+) m/z (%): 418 (100, $[M-H]^+$). Anal. Calcd. for $C_{22}H_{20}F_3NO_2S$ (419.46).

2-(4-(trifluoromethyl)phenylamino)-3-(nonylthio)naphthalene-1,4-dione (**5c**). It was synthesized from 2-(4-(trifluoromethyl)phenylamino)-3-chloronaphthalene-1,4-dione (**3a**) and nonane-1-thiol (**4c**) as an orange powder by using the general procedure. Yield: 0.047 g, 35%; mp 71-72 °C. FTIR (ATR) ν(cm^{-1}): 3328 (-NH), 3074 ($CH_{arom.}$), 2926, 2857 ($CH_{aliph.}$), 1669, 1651 (C=O), 1604, 1556 (C=C). ^{1}H NMR (500 MHz, *CDCl₃*) δ (ppm): 8.18-8.16 dd, *J: 7.81, 1.46 Hz*, 1H (-CH_{arom}); 8.12-8.07 dd, *J: 7.81, 1.46 Hz*, 1H (-CH_{arom}); 7.82 br s, 1H (-NH); 7.78-7.75 td, *J: 7.81, 1.46 Hz*, 1H (-CH_{arom}); 7.73-7.69 td, *J: 7.81, 1.47 Hz*, 1H (-CH_{arom}); 7.63-7.56 d, *J: 8.30 Hz*, 2H (-CH_{arom}); 7.09-7.03 d, *J: 8.78 Hz*, 2H (-CH_{arom}); 2.65-2.57 t, *J: 7.32 Hz*, 2H (S-CH_2-); 1.42-1.33 m, 2H (-CH_2-); 1.31-1.12 m, 12H (-CH_2); 0.51-

0.30 t, J: 7.32 Hz, 3H (-CH_3). ^{13}C NMR (125 MHz, *$CDCl_3$*) δ(ppm): 181.1, 180.1, 143.4, 141.4, 134.6, 133.3, 133.1, 130.6, 127.0, 126.7, 125.7, 125.6, 122.0, 121.1, 33.7, 31.8, 29.4, 29.3, 29.2; 29.0; 28.6, 22.6, 14.1. MS (ESI+) *m/z* (%): 476 (100, $[M+H]^+$). Anal. Calcd. for $C_{26}H_{28}F_3NO_2S$ (475.57).

2-(3-(trifluoromethyl)phenylamino)-3-(propylthio)naphthalene-1,4-dione (**5d**). It was synthesized from 2-(3-(trifluoromethyl)phenylamino)-3-chloronaphthalene-1,4-dione (**3b**) and propane-1-thiol (**4a**) as an orange powder by using the general procedure. Yield: 0.063 g, 56%, mp 100-101 °C. FTIR (ATR) ν(cm^{-1}): 3280 (-NH), 3081 ($CH_{arom.}$), 2933, 2833 ($CH_{aliph.}$), 1670, 1641 (C=O), 1599, 1524 (C=C). ^{1}H NMR (500 MHz, *$CDCl_3$*) δ (ppm): 8.18-8.16 dd, *J: 7.32, 0.98 Hz*, 1H (-CH_{arom}); 8.12-8.07 dd, *J: 7.32, 0.97 Hz*, 1H (-CH_{arom}); 7.86 s, 1H (-NH); 7.76-7.73 td, *J: 7.32, 1.47 Hz*, 1H (-CH_{arom}); 7.72-7.65 td, *J: 7.32, 0.97 Hz*, 1H (-CH_{arom}); 7.49-7.42 t, *J: 7.81 Hz*, 1H (-CH_{arom}); 7.42-7.37 d, *J: 7.81 Hz*, 1H (-CH_{arom}); 7.28 s, 1H (-CH_{arom}); 7.20-7.15 d, J: 7.81 Hz, 1H (-CH_{arom}); 2.63-2.55 t, *J: 7.32 Hz*, 2H (S-CH_2-); 1.45-1.35 h, J: 7.32 Hz, 2H (-CH_2-); 0.87-0.76 t, *J: 7.32 Hz* 3H (-CH_3). ^{13}C NMR (125 MHz, *$CDCl_3$*) δ(ppm): 181.0, 180.2, 144.1, 138.9, 134.6, 133.4, 133.0, 130.5, 128.9, 127.0, 126.7, 125.1, 120.8, 120.2, 118.8, 35.7, 22.8, 13.2. MS (ESI+) *m/z* (%): 392 (100, $[M+H]^+$). Anal. Calcd. for $C_{20}H_{16}F_3NO_2S$ (391.41).

2-(3-(trifluoromethyl)phenylamino)-3-(pentylthio)naphthalene-1,4-dione (**5e**). It was synthesized from 2-(3-(trifluoromethyl)phenylamino)-3-chloronaphthalene-1,4-dione (**3b**) and pentane-1-thiol (**4b**) as red oil by using the general procedure. Yield: 0.078 g, 66%. FTIR (ATR) ν(cm^{-1}): 3286 (-NH), 3082 ($CH_{arom.}$), 2930, 2868 ($CH_{aliph.}$), 1686, 1650, (C=O), 1614, 1536 (C=C). ^{1}H NMR (500 MHz, *$CDCl_3$*) δ (ppm): 8.20-8.18 dd, *J: 7.42, 1.23 Hz*, 1H (-CH_{arom}); 8.14-8.12 dd, *J: 7.55,1.11 Hz*, 1H (-CH_{arom}); 7.84 s, 1H (-NH); 7.80-7.76 td, *J: 7.54, 1.44 Hz*, 1H (-CH_{arom}); 7.74-7.70 td, *J: 7.51, 1.38 Hz*, 1H (-CH_{arom}); 7.50-7.46 t, *J: 7.81 Hz*, 1H (-CH_{arom}); 7.43-7.41 d, *J: 7.78 Hz*, 1H (-CH_{arom}); 7.29 s, 1H (-CH_{arom}), 7.20-7.18 d, *J: 7.90 Hz*, 1H (-CH_{arom}); 2.63-2.59 t, *J: 7.35 Hz*, 2H (-SCH_2); 1.42-1.20 m, 6H (-CH_2-); 0.84-0.81 t, *J: 7.0 Hz*, 3H (-CH_3). ^{13}C NMR (125 MHz, *$CDCl_3$*) δ(ppm): 181.1, 180.2, 144.0, 138.8, 134.7, 133.4, 133.0, 130.6, 128.9, 127.0, 126.8, 125.0, 120.8, 120.4, 118.7, 33.8, 30.8; 29.0, 22.1, 13.8. MS (ESI+) *m/z* (%): 420 (100, $[M+H]^+$). Anal. Calcd. for $C_{22}H_{20}F_3NO_2S$ (419.46).

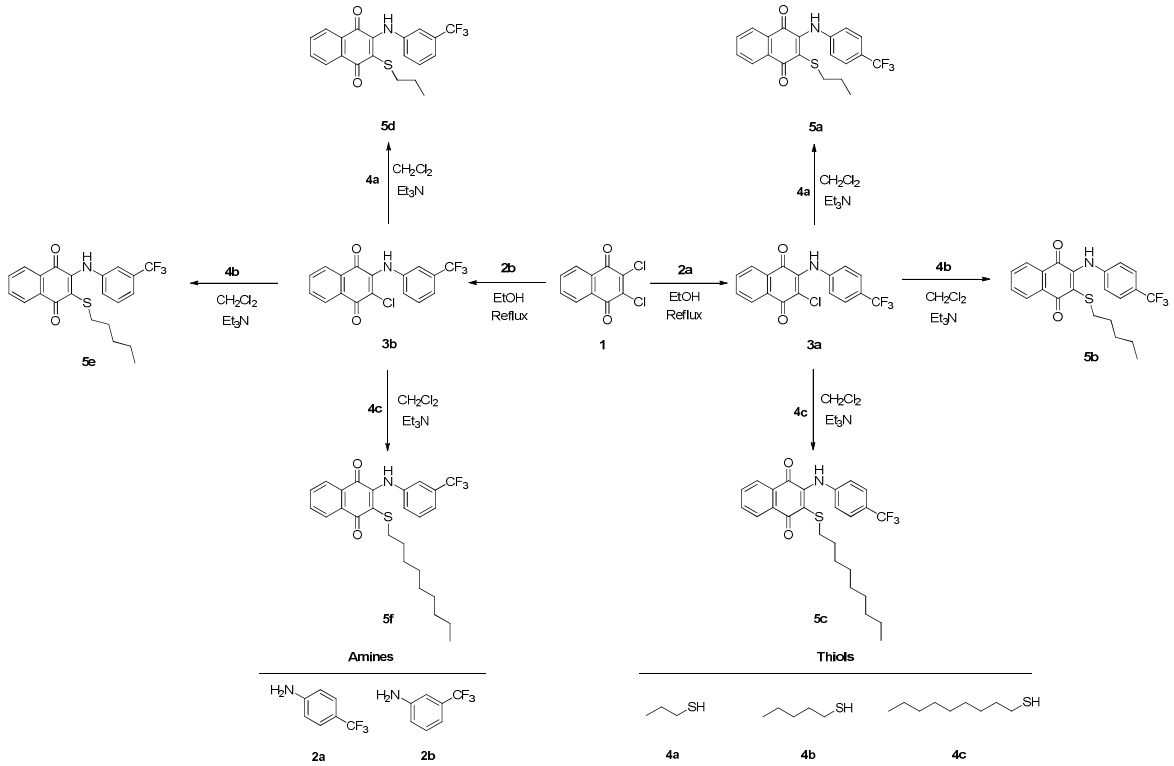
2-(3-(trifluoromethyl)phenylamino)-3-(nonylthio)naphthalene-1,4-dione (**5f**). It was synthesized from 2-(3-(trifluoromethyl)phenylamino)-3-chloronaphthalene-1,4-dione (**3b**) and nonane-1-thiol (**4c**) as red oil by using the general procedure. Yield: 0.096 g, 71 %. FTIR

(ATR) ν(cm^{-1}): 3289 (-NH), 3086 ($CH_{arom.}$), 2928, 2861 ($CH_{aliph.}$), 1671, 1641 (C=O), 1604, 1514 (C=C). ^{1}H NMR (500 MHz, *$CDCl_3$*) δ (ppm): 8.20-8.18 dd, *J: 7.59, 0.88 Hz*, 1H (-CH_{arom}); 8.14-8.12 dd, *J: 7.56, 0.90 Hz*, 1H (-$CH_{arom.}$); 7.84 s, 1H (-NH); 7.80-7.76 td, *J: 7.54, 1.41 Hz*, 1H (-CH_{arom}); 7.74-7.70 td, *J: 7.51, 1.35 Hz*, 1H (-$CH_{arom.}$); 7.50-7.46 t, *J: 7.85 Hz*, 1H (-$CH_{arom.}$); 7.43-7.41 d, *J: 7.80 Hz*, 1H (-$CH_{arom.}$); 7.29 s, 1H (-$CH_{arom.}$); 7.19-7.17 d, J: 7.90 Hz, 1H (-CH_{arom}.) 2.63-2.59 t, *J: 7.40 Hz*, 2H (-SCH_2); 1.41-1.18 m, 14H (-CH_2-); 0.91-0.87 t, *J: 7.86 Hz*, 3H (-CH_3). ^{13}C NMR (125 MHz, *$CDCl_3$*) δ(ppm): 181.1, 180.2, 144.0, 138.8, 134.6, 133.4, 133.0, 130.6, 128.9, 127.0, 126.7, 125.0, 120.8, 120.4, 118.8, 33.8, 31.8, 29.7, 29.4, 29.2, 29.0, 28.6, 22.6, 14.1. MS (ESI+) *m/z* (%): 474 (100, $[M-H]^+$). Anal. Calcd. for $C_{26}H_{28}F_3NO_2S$ (475.57).

RESULTS AND DISCUSSION

In order to prepare new straight-chained sulfanyl quinone precursors containing an aryl amine with electron donating group as trifluoromethyl at meta or para positions, 2-(4-(trifluoromethyl)phenylamino)-3-chloronaphthalene-1,4-dione (**3a**) and 2-(3-(trifluoromethyl)phenylamino)-3-chloronaphthalene-1,4-dione (**3b)** were obtained as starting compounds by means of nucleophilic substitution reactions of 2,3-dichloro-1,4-naphthoquinone (**1**) with arylamines containing trifluoromethyl group at meta and para positions (**2a, 2b**) by the method previously reported (20-22). The reaction involves replacing the chlorine atom present at the 2-position of 2,3 dicloro 1,4 naphthoquinone with an amine functional group. Nucleophilic substitution reaction of 2,3-dichloronaphthalene-1,4-dione (**1**) with primary aryl amines (**2a, 2b**) in ethanol resulted in the synthesis of 2-(arylamino)-3-chloro-naphthalene-1,4-diones (**3a, 3b**). Trifluoromethyl substituted amino chloro quinone substrates proved to be compatible with further nucleophilic reaction protocols due to chlorine atom in the structure which is differentiable functional group to allow easy manipulations of the molecular architecture. Compounds **3a** and **3b** are efficient new sulfanyl quinone precursors and possible synthones for new quinone derivatives. Reactions of **3a** and **3b** with propane, pentane, and nonane derivatives of aliphatic sulphanyl compounds lead to the formation of novel straight-chained sulfanyl arylamino-1,4- naphthoquinones (**5a-f**) in good yields. The reactions were performed at room temperature using a base like previous studies (2) and the reaction products were separated by column chromatography using eluents of varying polarity chloroform with hexane. The structures of the new members were identified by using spectroscopic analyses. The FTIR spectra of **5a-f** showed two strong signals between 1681 and 1641 cm^{-1} for the carbonyl groups of the naphthoquinone moieties. The ^{1}H NMR

spectra of **5a-f** exhibited d, dd, t and td at 8.20 - 7.02 ppm for the aromatic groups, a singlet at around 7.82-7.86 ppm for the protons of the amine group, triplets at 2.55 - 2.65 ppm for methylene protons of SCH_2 groups, multiplet at 1.18-1.49 and hextet 1.35-1.45 for other methylene protons **5a-c**, **5e-f** and **5d**, respectively, triplets at 0.30 - 0.91 ppm for the methyl protons. In the ^{13}C NMR spectrum we can easily note the presence of methyl carbons around 13.2-14.1, CH_2 carbons around 22.1-35.7 ppm, carbonyl carbons around 180.1-181.2 for quinone skeleton and C=C carbons around 118.7-143.7, as well as aromatic carbons from the naphthoquinone and aromatic amines introduced.



Scheme 1. Synthesized straight-chained sulfanyl 1,4-naphthoquinone derivatives substituted with aryl amines containing trifluoromethyl group.

CONCLUSION

The initial goal of our investigation was to synthesize the starting compounds 2-(4-(trifluoromethyl)phenylamino)-3-chloronaphthalene-1,4-dione (**3a**) and 2-(3-(trifluoromethyl)phenylamino)-3-chloronaphthalene-1,4-dione (**3b**) from the reactions of **1** with arylamines (**2a, 2b**). After that, our attention was turned to preparing novel straight-chained sulfanyl arylamino-1,4- naphthoquinones (**5a-f**) by using **3a** and **3b** and aliphatic

sulfanyl compounds (**4a**, **4b, 4c**). Based on what has been described about the importance of naphthoquinone derivatives, the main objective of this study was the development of new straight-chained sulfanyl amino naphthoquinones having an aryl amine with trifluoromethyl group at meta and para positions that may have potential pharmaceutical value.

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