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Synthesis of Novel Thio-Substituted Aminonaphthoquinones

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Abstract

Novel thio-substituted aminonaphthoquinones were synthesized by the reactions of 2-(4-(trifluoromethyl)phenylamino)-3-chloronaphthalene-1,4-dione (**3a**) and 2-(3-(trifluoromethyl)phenylamino)-3-chloronaphthalene-1,4-dione (**3b**) with various thiol compounds such as ethanethiol (**4a**), methyl 2-mercaptoacetate (**4b**), ethyl 2-mercaptoacetate (**4c**). 2,3-dichloro-1,4-naphthoquinone (**1**) was reacted with aryl amines (**2a, 2b**) containing trifluoromethyl group to give compounds **3a** and **3b** by applying a method published in literature. Finally, obtained novel compounds (**5a-5f**) were characterized via IR, ^{1}H NMR, ^{13}C NMR, and MS techniques. Based on previous studies in the literature, it is expected that some potential biological activities of new compounds could find application in medicinal chemistry.

Keywords: Aminonaphthoquinone, 1,4-naphthoquinone, thiol, aryl amine, trifluoromethyl group, CF_3, electron withdrawing group, nucleophilic substitution.

1. INTRODUCTION

Among the quinoid structures, naphthoquinones appear as a remarkable subclass owing to their diverse biological responses which exhibit a wide range of biological activities such as antimalarial, anticancer, antibacterial, antifungal, antiparasitic, antithrombotic, antiviral, antiallergic, anti-inflammatory, antiplatelet, anti-ringworm, radical scavenging, apoptosis and lipoxygenase type of activity [1-25]. Naphthalene-like naphthoquinone structures, which bear a benzene ring and a cyclic diketone, are redox-active compounds generating oxygen species.

Therefore, above-mentioned structures have attracted great attention in the field of drug discovery and new medicine development in medicinal chemistry [26-29]. On the other hand, the isolation, synthesis and reactions of some bioactive naphthoquinone compounds have been reported and also the biosynthesis of a naphthoquinone derivative, vitamin K, was discussed briefly and given references therein [30-37].
The insertion of strong electron-withdrawing perfluoroalkyl moieties into organic compounds changes their physiochemical and chemical properties, especially a distortion in the molecule occurs because of their bulky structure with steric hindrance [31, 38-41]. Recently, various synthetic methods have attracted a considerable attention to introduce perfluoroalkyl functional groups to the organic fragments [42-44]. Since trifluoromethyl groups and amino naphthoquinones are known as desirable structures in medicinal chemistry due to their interesting properties which contribute to the biological activity and drug development, Li *et al*. have recently carried a synthesis out to add directly a trifluoromethyl moiety into 2-amino-1,4-naphthoquinone at room temperature in air [45].

The developed new method has been successful and a number of synthesized compounds have exhibited antiproliferative activity. Therefore, the introduction of a trifluoromethyl group to amino naphthoquinones has been suggested as a promising approach for pharmacological applications against cancer [45].

Recently, sulfanyl and trifluoromethyl containing aryl amine substituted 1,4-naphthoquinones have been synthesized and characterized successfully [46-48]. The different influences of the -CF_3 group position in aryl amine ring of the newly prepared compounds were clearly elucidated and the molecular docking studies have also supported the experimental results. Some of these compounds were reported as promising antibacterial and

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antimicrobial agents [46]. In this respect, herein, novel trifluoromethyl bearing nitrogen- and sulfur-substituted 1,4-naphthoquinone compounds have been prepared and characterized, expecting that the new structures contribute to researches in the literature on biological activity desired investigations and applications.

2. MATERIALS AND METHODS

Commercial materials obtained from different suppliers were used directly in all experiments. Thin-layer chromatography (TLC) technique was adopted to follow the progress of reactions by using analytical TLC plates (aluminium based DC-plates) which were supplied from Merck KGaA (silica gel 60 F254). TLC plates were checked under 254 nm-UV light. To separate and/or purify the compound(s), column chromatography technique was implemented by means of silica gel 60 (Merck, 63-200 μm particle size, 60–230 mesh).

A Varian UNITY INOVA instrument (^{1}H NMR frequency: 500 MHz and ^{13}C NMR frequency: 125 MHz) was used to obtain NMR spectra recorded in $CDCl_3$ as solvent and its signals appeared at δ 7.19 ppm (^{1}H NMR) and δ 76.0 ppm (^{13}C NMR). For the identification and splitting of NMR peaks, s, br s, d, t, q, dd, td and m stand for singlet, broad singlet, doublet, triplet, quartet, doublet of doublets, triplet of doublets and multiplet, respectively. In ppm (δ) relative to TMS were shown the chemical shifts and in hertz (Hz) were given the coupling constants (J). Infrared spectrums were recorded as ATR on a Perkin Elmer Spectrum 100 Optical FT-IR Spectrometer.

The mass spectra were obtained on a BRUKER Microflex LT by MALDI (Matrix Assisted Laser Desorption Ionization)-TOF technique via addition of 1,8,9-anthracenetriol (DIT, dithranol) as matrix. A Stuart SMP-10 melting point apparatus was used to determine the melting points (mp) that were uncorrected.

Standard Method for Preparation of the Chloro-substituted Aminonaphthoquinone Compounds (3a-3b)

2,3-Dichloro-1,4-naphthoquinone (1) reacted with trifluoromethyl substituted aryl amines (2a-2b) to form 2-arylamino-3-chloro-1,4-naphthoquinone compounds (3a-3b, Scheme 1) by applying a method from the previously reported publications and cited references therein [49-51].

Standard Method for Preparation of the Thio-substituted Aminonaphthoquinone Compounds (5a-5f)

The standard method was adapted from the literature [52]. The chloro-substituted aminonaphthoquinone compounds (3a-3b) and various thiol compounds (4a, 4b, 4c) in CH_2Cl_2 were stirred at room temperature by addition of Et_3N. The extraction of the reaction product was performed with $CHCl_3$. After that, it was washed with distilled H_2O and dried over $CaCl_2$. The solvent was evaporated under vacuum. Column chromatography on silica gel using $CHCl_3$ for 5a, 5b, 5d, 5f and CH_2Cl_2 for 5c, 5e was conducted for the crude product to give the separated and purified products (5a-5f, scheme 1).

2-(Ethylthio)-3-((4-(trifluoromethyl)phenylamino)naphthalene-1,4-dione (5a): 2-Chloro-3-((4-(trifluoromethyl)phenylamino)naphthalene-1,4-dione (3a) and ethanethiol (4a) were reacted to yield the 5a as red powder by applying the standard method. Yield: 0.047 g, 44%; mp 120-121 °C. FTIR (ATR) ν(cm^{-1}): 3340 (-NH), 3067 (CH_{arom}), 2928, 2872 ($CH_{aliphatic}$), 1658, 1644 (C=O), 1615, 1586 (C=C). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 8.17 dd, *J*:7.81, 0.97 Hz, 1H (-CH_{arom}); 8.11 dd, *J*:7.32, 0.98 Hz, 1H (-CH_{arom}); 7.82 br s, 1H (-NH); 7.77 td, *J*:7.81, 1.46 Hz, 1H (-CH_{arom}); 7.71 td, *J*: 7.32, 1.46 Hz, 1H (-CH_{arom}); 7.59 d, *J*: 8.30 Hz, 2H (-CH_{arom}); 7.06 d, *J*: 8.30 Hz, 2H (-CH_{arom}); 2.67 q, *J*:7.32 Hz, 2H (S-CH_2-); 1.08 t, *J*:7.32 Hz, 3H (-CH_3). ^{13}C NMR (125 MHz, $CDCl_3$) δ(ppm): 181.2, 180.1, 143.6, 141.5, 134.6, 133.3, 133.2, 130.6, 127.0, 126.8, 125.8, 125.7, 125.6, 125.2, 121.6, 121.1, 27.9, 14.6. MS MALDI TOF (m/z): Calc.: 377.070, Found: 377 [M]$^+$.

Methyl 2-((1,4-dioxo-3-((4-(trifluoromethyl)phenylamino)-1,4-dihydronaphthalen-2-yl)thio)acetate (5b): 2-Chloro-3-((4-(trifluoromethyl)phenylamino)naphthalene-1,4-dione (3a) and methyl 2-mercaptoacetate (4b) were reacted to yield the 5b as dark red oil by applying the standard method. Yield: 0.099 g, 82%. FTIR (ATR) ν(cm^{-1}): 3459 (-NH), 3296 (CH_{arom}), 3000, 2954, 2848 ($CH_{aliphatic}$), 1730 (C=O), 1592, 1557 (C=C). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 8.15 dd, *J*: 7.32, 0.98 Hz, 1H (-CH_{arom}); 8.08 dd, *J*: 7.81, 0.98 Hz, 1H (-CH_{arom}); 8.00 br s, 1H (-NH); 7.75 td, *J*: 7.81, 1.47 Hz, 1H (-CH_{arom}); 7.70 td, *J*: 7.32, 0.98 Hz, 1H (-CH_{arom}); 7.58 d, *J*: 8.79 Hz, 2H (-CH_{arom}); 7.10 d, *J*: 8.30 Hz, 2H (-CH_{arom}); 3.76 s, 3H (O-CH_3); 3.59 s, 2H (S-CH_2-). ^{13}C NMR (125 MHz, $CDCl_3$) δ(ppm): 180.6, 179.9, 169.8, 169.7, 145.6, 142.2, 134.8, 133.3, 133.1, 130.6, 130.1, 130.0, 126.0, 125.9, 121.9, 117.9, 52.6, 35.1, 29.7. MS MALDI TOF (m/z): Calc.: 421.060, Found: 421 [M]$^+$.

Ethyl 2-((1,4-dioxo-3-((4-(trifluoromethyl)phenylamino)-1,4-dihydronaphthalen-2-yl)thio)acetate (5c): 2-Chloro-3-((4-(trifluoromethyl)phenylamino)naphthalene-1,4-dione (3a) and ethyl 2-mercaptoacetate (4c) were reacted to yield the 5c as a red powder by applying the standard method. Yield: 0.008 g, 6%; mp 75-76 °C. FTIR (ATR) ν(cm^{-1}): 3276 (-NH), 3071 (CH_{arom}), 2955, 2916, 2848 ($CH_{aliphatic}$), 1718, 1671, 1632 (C=O), 1590, 1545 (C=C). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 8.18 dd, *J*: 7.81, 0.97 Hz, 1H (-CH_{arom}); 8.10 dd, *J*: 7.81, 0.97 Hz, 1H (-CH_{arom}); 7.99 br s, 1H (-NH); 7.78 td, *J*: 7.81, 1.47 Hz, 1H (-CH_{arom}); 7.71 td, *J*: 7.81, 1.46 Hz, 1H (-CH_{arom}); 7.60 d, *J*: 8.79 Hz, 2H (-CH_{arom}); 7.11 d, *J*: 8.29 Hz, 2H (-CH_{arom}); 4.03 q, *J*: 7.32 Hz, 2H (O-CH_2-); 3.55 s, 2H (S-CH_2-); 1.15 t, *J*: 6.83 Hz, 3H (-CH_3). ^{13}C NMR (125 MHz, $CDCl_3$) δ(ppm): 180.6, 179.9, 169.2, 145.6, 142.2, 134.8, 134.6, 134.2, 133.3, 133.2, 130.6, 128.2, 127.0, 126.9, 126.1, 126.0, 121.8, 118.2, 61.5, 29.7, 14.1. MS MALDI TOF (m/z): Calc.: 435.075, Found: 435 [M]$^+$.

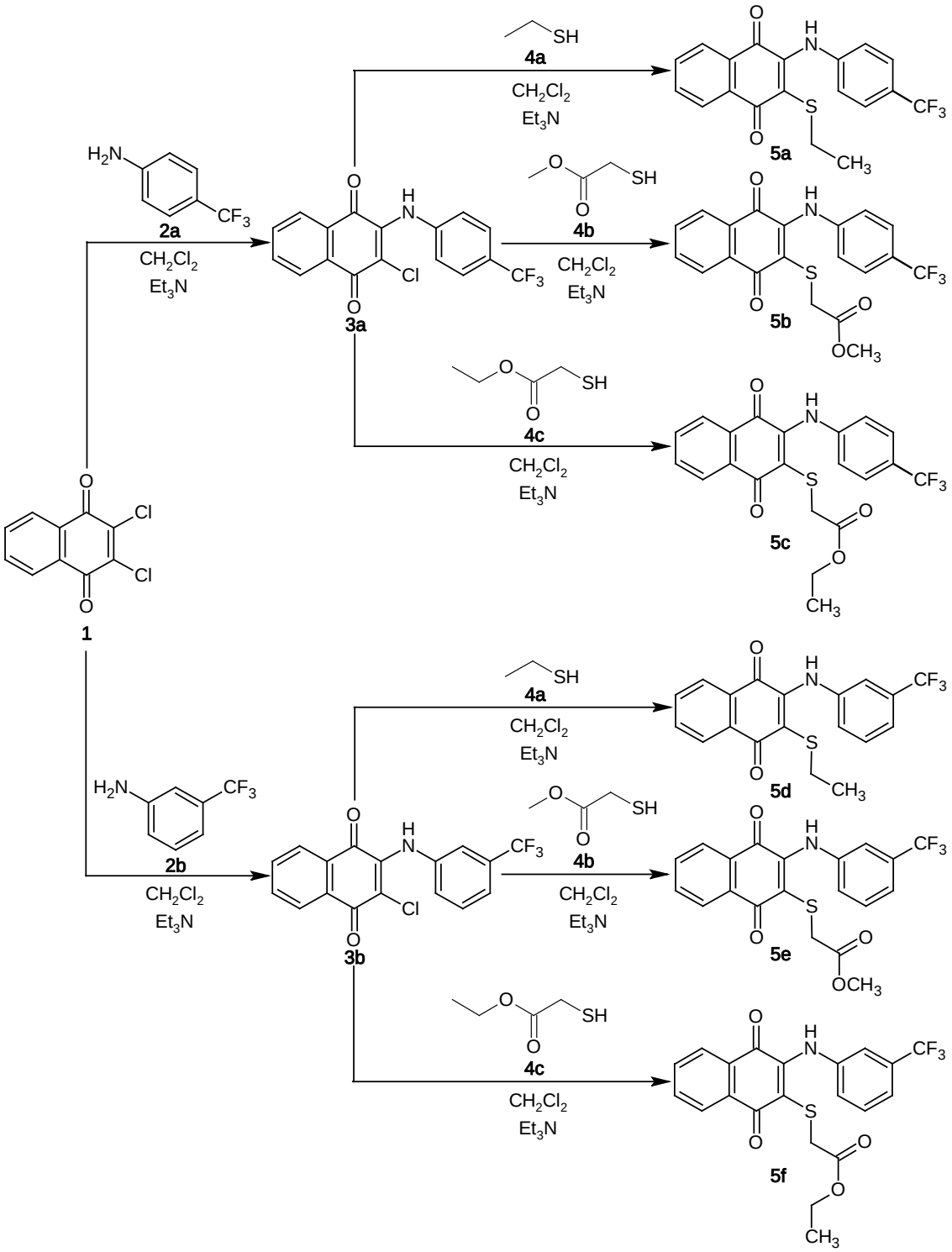
2-(Ethylthio)-3-((3-(trifluoromethyl)phenylamino)naphthalene-1,4-dione (5d): 2-Chloro-3-((3-(trifluoromethyl)phenylamino)naphthalene-1,4-dione (3b) and ethanethiol (4a) were reacted to yield the 5d as red powder by applying the standard method. Yield: 0.054 g, 51%; mp 123-124 °C. FTIR (ATR) ν(cm^{-1}): 3282 (-NH), 3076 (CH_{arom}), 2962, 2929 ($CH_{aliphatic}$), 1664, 1635 (C=O), 1591, 1522 (C=C).^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 8.16 dd, *J*: 7.81, 1.46 Hz, 1H (-CH_{arom}); 8.10 dd, *J*: 7.81, 1.46 Hz, 1H (-CH_{arom}); 7.85 br s, 1H (-NH); 7.76 td, *J*: 7.32, 1.46 Hz, 1H (-CH_{arom}); 7.70 td, *J*: 7.32, 1.46 Hz, 1H (-CH_{arom}); 7.46 t, *J*: 7.81 Hz, 1H (-CH_{arom}); 7.40 d, *J*: 7.81 Hz, 1H (-CH_{arom}); 7.28 s, 1H (-CH_{arom}); 7.18 d, *J*: 8.30 Hz, 1H (-CH_{arom}); 2.66 q, *J*: 7.81 Hz, 2H (S-CH_2-); 1.06 t, *J*: 7.32 Hz, 3H (-CH_3). ^{13}C NMR (125 MHz, $CDCl_3$) δ(ppm): 181.1, 180.2, 144.1, 138.9, 134.6, 133.4, 133.0, 130.5, 131.0, 128.9, 127.0, 126.7, 125.1, 120.9, 120.8, 119.9, 118.8, 28.0, 14.4. MS MALDI TOF (m/z): Calc.: 377.070, Found: 377 $[M]^+$.

Methyl 2-((1,4-dioxo-3-((3-(trifluoromethyl)phenylamino)-1,4-dihydronaphthalen-2-yl)thio)acetate (5e): 2-Chloro-3-((3-(trifluoromethyl)phenylamino)naphthalene-1,4-dione (3b) and methyl 2-mercaptoacetate (4b) were reacted to yield the 5e as a dark red powder by applying the standard method. Yield: 0.057 g, 47%; mp 116-117 °C. FTIR (ATR) ν(cm^{-1}): 3275 (-NH), 3111 (CH_{arom}), 2959, 2924, 2852 ($CH_{aliphatic}$), 1735, 1682 (C=O), 1623, 1592 (C=C). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 8.17 dd, *J*: 7.81, 0.98 Hz, 1H (-CH_{arom}); 8.10 dd, *J*: 7.81, 0.98 Hz, 1H (-CH_{arom}); 8.01 br s, 1H (-NH); 7.78 td, *J*: 7.32, 0.98 Hz, 1H (-CH_{arom}); 7.70 td, *J*: 7.32, 0.98 Hz, 1H (-CH_{arom}); 7.49-7.43 m, 2H (-CH_{arom}); 7.33 s, 1H (-CH_{arom}); 7.23 d, *J*: 7.80 Hz, 1H (-CH_{arom}); 3.63 s, 3H (O-CH_3); 3.54 s, 2H (S-CH_2-). ^{13}C NMR (125 MHz, $CDCl_3$) δ(ppm): 180.6, 179.9, 169.7, 146.1, 139.6, 134.8, 133.3, 133.0, 131.1, 130.6, 129.3, 127.0, 126.9, 125.9, 121.6, 119.6, 116.4, 52.5, 35.2, 29.7. MS MALDI TOF (m/z): Calc.: 421.060, Found: 421 $[M]^+$.

Ethyl 2-((1,4-dioxo-3-((3-(trifluoromethyl)phenylamino)-1,4-dihydronaphthalen-2-yl)thio)acetate (5f): 2-Chloro-3-((3-(trifluoromethyl)phenylamino)naphthalene-1,4-dione (3b) and ethyl 2-mercaptoacetate (4c) were reacted to yield the 5f as dark red oil by applying the standard method. Yield: 0.011 g, 9%. FTIR (ATR) ν(cm^{-1}): 3295 (-NH), 3074 (CH_{arom}), 2985, 2925, 2851 ($CH_{aliphatic}$), 1730, 1667 (C=O), 1591,1556 (C=C). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 8.18 dd, *J*: 7.81, 1.47 Hz, 1H (-CH_{arom}); 8.10 dd, *J*: 7.81, 0.97 Hz, 1H (-CH_{arom}); 8.00 br s, 1H (-NH); 7.78 td, *J*: 7.81, 1.47 Hz, 1H (-CH_{arom}); 7.70 td, *J*: 7.81, 1.46 Hz, 1H (-CH_{arom}); 7.49-7.43 m, 2H (-CH_{arom}); 7.32 s, 1 H (-CH_{arom}); 7.22 d, *J*: 7.32 Hz, 1H (-CH_{arom}); 4.07 q, *J*: 7.32 Hz, 2H (O-CH_2-); 3.52 s, 2H (S-CH_2-); 1.15 t, *J*: 6.83 Hz, 3H (-CH_3). ^{13}C NMR (125 MHz, $CDCl_3$) δ(ppm): 180.6, 179.9, 169.2, 146.0, 139.6, 134.8, 133.4, 133.0, 131.4, 131.1, 130.6, 129.3, 127.0, 126.9, 125.7, 121.5, 119.5, 116.8, 61.5, 29.7, 14.0. MS MALDI TOF (m/z): Calc.: 435.075, Found: 435 $[M]^+$.

3. RESULTS AND DISCUSSION

Precursors of novel thio-substituted aminonaphthoquinone compounds were prepared by performing nucleophilic substitution reactions of 2,3-dichloro-1,4-naphthoquinone (1) with trifluoromethyl group substituted aryl amines (2a, 2b) applying preparation method previously explained in the literature [50-51] and shown in Scheme 1. In these reactions, one chlorine atom of 2,3-dichloro-1,4-naphthoquinone (1) was substituted with primary aryl amines (2a, 2b) in ethanolic medium yielding 2-arylamino-3-chloro-1,4-naphthoquinone compounds (3a-3b). Since compounds 3a and 3b still contain one chlorine atom, they can easily give different nucleophilic substitution products with various functional group, e.g. thiols. The reactions with thiols resulted in nitrogen, sulfur, and trifluoromethyl group containing 1,4-naphthoquinone structures. Various thiol compounds, such as ethanethiol (4a), methyl 2-mercaptoacetate (4b), ethyl 2-mercaptoacetate (4c) reacted with 3a and 3b to yield novel sulfanyl substituted aminonaphthoquinone derivatives, 2-(ethylthio)-3-((4-(trifluoromethyl)phenyl)amino)naphthalene-1,4-dione (5a), methyl 2-((1,4-dioxo-3-((4-(trifluoromethyl)phenyl)amino)-1,4-dihydronaphthalen-2-yl)thio)acetate (5b), ethyl 2-((1,4-dioxo-3-((4-(trifluoromethyl)phenyl)amino)-1,4-dihydronaphthalen-2-yl)thio)acetate (5c), 2-(ethylthio)-3-((3-(trifluoromethyl)phenyl)amino)naphthalene-1,4-dione (5d), methyl 2-((1,4-dioxo-3-((3-(trifluoromethyl)phenyl)amino)-1,4-dihydronaphthalen-2-yl)thio)acetate (5e), ethyl 2-((1,4-dioxo-3-((3-(trifluoromethyl)phenyl)amino)-1,4-dihydronaphthalen-2-yl)thio)acetate (5f) in reasonable yields. The experiments were carried out at room temperature by addition a base (triethylamine, $(C_2H_5)_3N$) as performed in previous studies (52). Chloroform and dichloromethane were used during column chromatography technique for separation and purification of crude products after reactions. A number of spectroscopic methods were utilized to characterize novel compounds of 5a-5f (Scheme 1). In the ^{1}H NMR spectra, doublets, doublet of doublets, triplets and triplet of doublets at 8.26-7.10 ppm for the aromatic protons of 5a-5f and a singlet at around 8.01-7.82 ppm for the amine hydrogen, quartets at 4.01-4.09 ppm for the –CH_2 protons of 5c and 5f which are adjacent to oxygen atom, singlets at 3.52-3.59 ppm for the –SCH_2 protons of 5b, 5c, 5e, 5f and quartets at 2.63-2.69 ppm for the -SCH_2 protons of 5a and 5d, triplets at 1.07-1.16 ppm for the methyl protons of 5a, 5c, 5d, 5f and singlets at 3.63 and 3.76 ppm for the methyl protons of 5b and 5e which are adjacent to oxygen atom were assigned. The ^{13}C NMR spectrum exhibited the peaks of methyl carbons around 14.0-29.7 ppm, methylene carbons around 27.9-65.1 ppm, carbonyl carbons around 179.9-181.2 ppm, carbon-carbon double bond and aromatic carbons around 116.4-146.1 ppm. The structure of novel compounds were also supported by MS results of 5a-5d (377 $[M]^+$), 5b-5e (421 $[M]^+$) and 5c-5f (435 $[M]^+$). The IR spectra of (5a-5f) showed characteristic carbonyl (C=O) signals between 1735 and 1632 cm^{-1} and (C=C) signals between 1623 and 1522 cm^{-1}.



Scheme 1. Preparation of various thio-substituted amino 1,4-naphthoquinone compounds containing highly electron withdrawing group.

4. CONCLUSION

To sum up, novel thio-substituted amino 1,4-naphthoquinone compounds (5a-5f) were synthesized and characterized by IR, ^{1}H NMR, ^{13}C NMR, and MS in the present work. Compounds 3a and 3b were also used as precursors in the preparation. Standard conditions were applied during experiments and reasonable yields were obtained. Since the new structures contain electron withdrawing trifluoromethyl group, highly electronegative nitrogen, oxygen and sulfur atoms and well-known role of 1,4-naphthoquinone moiety in pharmaceutical chemistry, it can be expected that novel compounds could potentially exhibit anticancer and antimicrobial biological type of activity. Considering the importance of these type of quinone compounds, future studies are being continued in our laboratory.

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