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DESIGN AND SYNTHESIS OF SOME PIPERAZINE HYBRID MOLECULES

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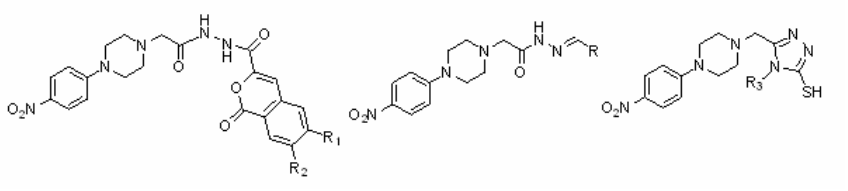
In this work, a new series of piperazine hybrid molecules containing coumarin, isatin, salicyl, furane and 1,2,4-triazol-3-thiol moieties was synthesized in good yields. 2-[4-(4-Nitrophenyl)piperazin-1-yl]acetohydrazide was used as key intermediate to obtain these hybrid molecules. The structures of newly synthesized compounds were identified by ^{1}H NMR, ^{13}C NMR and elemental analysis data.



INTRODUCTION

The Piperazines are a wide class of chemical compounds with many important pharmacological properties. Piperazines have the chemical similarity with piperidine, a constituent of piperazine in the black pepper plant (*Piper nigrum*). Piperazine was introduced to the medicine as a solvent for uric acid.[1-3] Also, piperazine ring has some advantages like low toxicity, easy formation of multiple hydrogen or ionic bonds, and acid–base equilibrium constant; all of these advantages make piperazine an essential pharmacophore for the drug design. Also, piperazine is a very important starting material for pharmaceutical chemistry.[4] Its derivatives have been studied by the researchers due to their biological properties (e.g. antiviral,[5] antibacterial,[6] anticancer,[7] antifungal[8] and so on).

Diversity of structural modifications on the piperazine ring has made piperazine derivatives indispensable anchors for the development of novel therapeutic agents.[9,10] Despite numerous attempts to develop new structural prototypes in search of medicinal chemistry, synthesis of hybrid molecules still remain as one of the most versatile method to obtain bioactive compounds. The structural modification of known molecules is a method widely used in drug research leading to identification of new compound prototypes that are more active, have satisfactory bioavailability, low toxicity, and proper metabolism in therapeutic use.[11-20]

Based on the above considerations, and in a continuation of our work on potential bioactive heterocycles, we described the synthesis some piperazine hybrid molecules containing coumarin, isatin, salicyl and 1,2,4-triazol-3-thiol moieties as potential bioactive agents.

RESULTS AND DISCUSSION

The main aim of the present study is the synthesis of new piperazine derivatives incorporating several heterocyclic moieties including coumarin, salicyl, furane, isatin, and/or 1,2,4-triazol-3-thiol. Synthesis of the intermediate and target compounds was

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performed according to the reactions outlined in Figures 1, 2, 3, 4 and 5. Initially, 4-nitrophenylpiperazine was reacted with ethyl bromoacetate in acetone to synthesize ethyl [4-(4-nitrophenyl)piperazin-1-yl]acetate (**1**). Then, this compound was reacted with hydrazine hydrate in ethanol to obtain 2-[4-(4-nitrophenyl)piperazin-1-yl]acetohydrazide (**2**),[21] which is the key intermediate to synthesize hybrid molecules (Figure 1).

Then, four salicyl aldehyde derivatives were treated with 2,2-dimethyl-1,3-dioxane-4,6-dione to obtain coumarin-3-carboxlic acid derivatives (**3a-d**). Then, these compounds were reacted with 1*H*-benzotriazole in dichloromethane to obtain coumarin containing benzotriazole derivatives (**4a-d**), which are the second intermediate to synthesize coumarin containing piperazine derivatives (Figure 2).

Secondly, 2-[4-(4-nitrophenyl)piperazin-1-yl]acetohydrazide (**2**) was reacted with compounds **4a-d** in ethanol to obtain coumarin containing piperazine derivatives (**5a-d**), (Figure 3). Literature searches have showed that benzotriazole group is an easy leaving group and this allows many synthetic applications. [13, 20] In this context, reaction of compounds **4a-d** and **2** afforded the target hybrid molecules (**5a-d**).

To synthesize N-acylhydrazones, 2-[4-(4-nitrophenyl)piperazin-1-yl]acetohydrazide (**2**) was reacted with isatin, salicyl aldehyde and furan-2-aldehyde (**6**, **7** and **8**), one by one, to obtain piperazine containing isatin, salicyl and furane moieties (Figure 4).

Lastly, isothiocyanate derivatives (**9a, b**) were obtained by the reaction of 2-[4-(4-nitrophenyl)piperazin-1-yl]acetohydrazide and methyl or p-fluorophenyl isothiocyanate. Then, these compounds were treated with NaOH to obtain piperazine containing 1,2,4-triazol-3-thiol derivatives (**10a, b**) (Figure 5).

Spectral investigations of newly synthesized compounds are in accordance with the proposed structures. In ^{1}H NMR spectra of compounds **5a-d**, two NH proton signals were shown at about 10.50 ppm although these proton signals were observed as one signal. Coumarin C-4 proton was observed at about 8.80 ppm as singlet. Two piperazine CH_2 protons were shown at about 3.30 and 3.20 ppm as multiplet. In ^{13}C NMR spectra of these compounds, coumarin C-2 and coumarin C-4 carbons were shown at about 167 and 148 ppm, respectively. Two hydrazide carbonyl were resonated at about 159 and 160 ppm. Two CH_2 signals were shown at about 52 and 46 ppm.

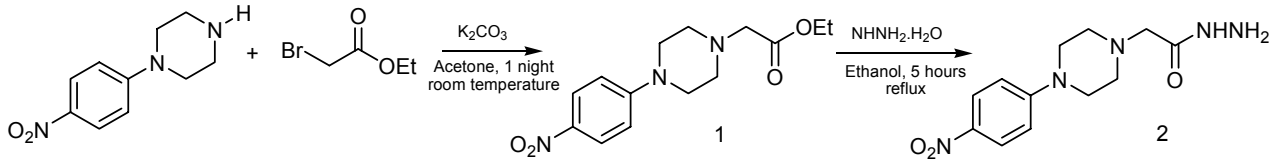

Fig. 1 – Synthesis of 2-[4-(4-nitrophenyl)piperazin-1-yl]acetohydrazide (**2**).

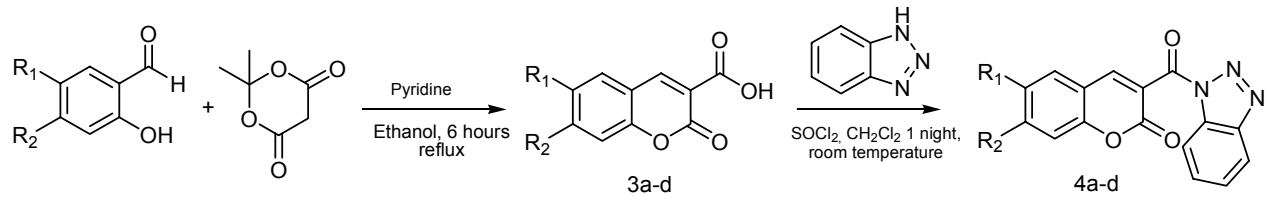

Fig. 2 – Synthesis of coumarin containing benzotriazole derivatives (**4a-d**).

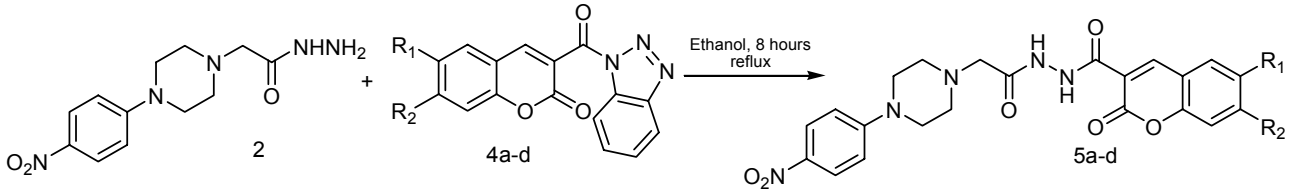

Fig. 3 – Synthesis of coumarin containing piperazine derivatives (**5a-d**).

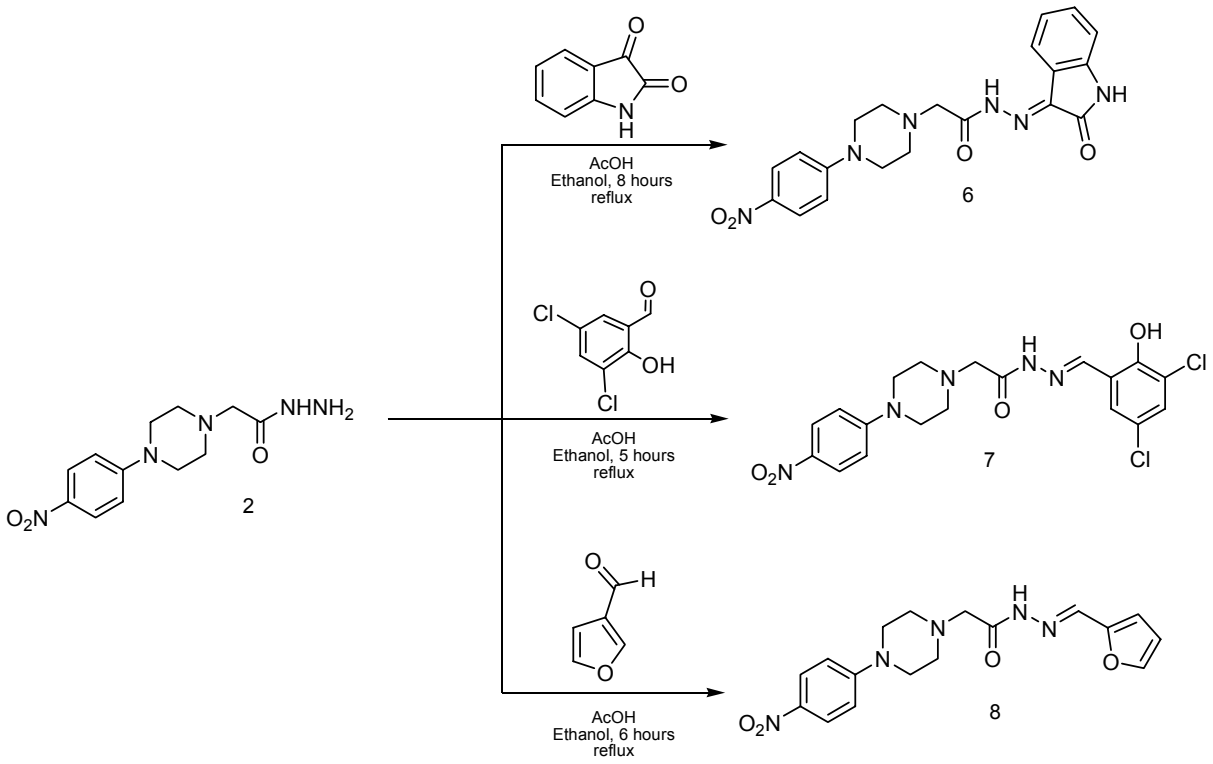

Fig. 4 – Synthesis of Schiff bases (**6, 7** and **8**).

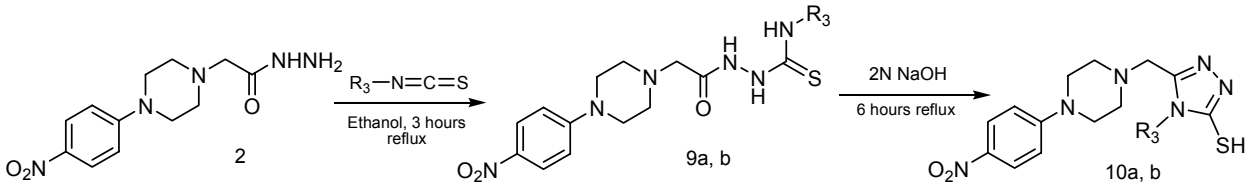

Fig. 5 – Synthesis of piperazine containing 1,2,4-triazol-3-thiol derivatives (**10a, b**).

In ^{1}H NMR spectra of schiff bases (compound **6**, **7** and **8**), NH and CH signals were shown at about 11.20 and 8.21 ppm, respectively. In ^{13}C NMR spectra of these compounds, C=O and N=CH signals were resonated at about 170 and 155 ppm, respectively. When ^{1}H-NMR spectra of these compounds have been compared, it has been seen that some of the protons have 2 sets of signal at different ppm. This is because of the compounds, which have arylene-hydrazide structure, exist as *E/Z* geometrical isomer from C=N double bond and *cis/trans* amide conformer at the CO-NH single bond. According to the literature, compounds which have C=N double bond prefers *E* geometrical isomer in DMSO-d_6 and *Z* isomers can be preferred in less polar solvents. Therefore, N-CH_2, N=CH and N-H signals were observed 2 sets of signals because of *cis/trans* conformer. The ratio in each case has been calculated by using ^{1}H NMR data.

In ^{1}H NMR spectra of isothiocyanate derivatives (**9a**, **b**), three NH signals were shown as two set of signals at about 10.0 and 9.50 ppm. In ^{13}C NMR spectra of these compounds, C=S was not observed. In ^{1}H NMR spectra of triazol-3-thiol derivatives (**10a, b**), SH signals were shown as singlet at about 14.0 ppm. Two C=N carbon signals were observed at about 155 and 150 ppm in ^{13}C NMR spectra of these compounds. Also, all compounds have suitable elemental analysis results with their structures.

EXPERIMENTAL

All the chemicals were supplied from Merck, Sigma-Aldrich, and Fluka. Melting points were taken in capillary tubes on a Stuart SMP30 melting point apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were acquired on a Varian Mercury 400 spectrometer (400 and 100 MHz, respectively) in DMSO-d_6, with TMS as internal standard. The

elemental compositions were determined on a Carlo Erba 1106 CHN analyzer; the experimental values were in agreement (±0.4%) with the calculated ones.

Synthesis of compounds 5a-d

A solution of 2-[4-(4-nitrophenyl)piperazin-1-yl]acetohydrazide (**2**) (0.01 mol) and compounds **4a-d** (0.011 mol) in ethanol (15 mL) were placed in a round-bottomed flask. The mixture was refluxed for 8 hours. After the reaction was completed (it was monitored by TLC, ethyl acetate/hexane, 3/1), the mixture was cooled to room temperature. The obtained solid was filtered off, washed with hot ethanol to obtain the pure product.

N'-{[4-(4-Nitrophenyl)piperazin-1-yl]acetyl-2-oxo-2H-chromene-3-carbohydrazide (**5a**): Yield: 3.29 g (73%). M.p. 260-261 °C, ^{1}H NMR (DMSO-d_6, 400 MHz), δ ppm: 10.47 (s, 2H, 2NH), 8.87 (s, 1H, coumarin-C_4-H), 8.02 (m, 4H, Ar-H), 7.74 (t, *J*=7.2 Hz, 1H, Ar-H), 7.50 (d, *J*=8.0 Hz, 1H, Ar-H), 7.44 (t, *J*=8.0 Hz, 1H, Ar-H), 7.03 (d, *J*=8.0 Hz, 2H, Ar-H), 3.49 (m, 4H, $2CH_2$), 3.18 (s, 2H, NCH_2), 2.65 (m, 4H, $2CH_2$). ^{13}C NMR (DMSO-d_6, 100 MHz), δ ppm: 167.37, 160.25, 159.71 (C=O), 155.13 (coumarin C-3), 154.40 (Ar-C), 148.54 (coumarin C-4), 137.24, 134.91, 130.82, 126.18 (2C), 125.70, 118.72, 116.71, 113.08 (2C) (Ar-C), 59.50 (NCH_2), 52.52 ($2CH_2$), 46.72 ($2CH_2$). Anal. Calcd. For $C_{22}H_{21}N_5O_6$: C, 58.53; H, 4.69 and N, 15.51; found C, 58.42; H, 4.61 and N, 15.40.

6-Chloro-N'-{[4-(4-nitrophenyl)piperazin-1-yl]acetyl}-2-oxo-2H-chromene-3-carbohydrazide (**5b**): Yield: 3.30 g (68%). M.p. 221-222 °C, ^{1}H NMR (DMSO-d_6, 400 MHz), δ ppm: 10.44 (s, 2H, 2NH), 8.82 (s, 1H, coumarin-C_4-H), 8.13 (s, 1H, Ar-H), 8.04 (d, *J*=8.8 Hz, 2H, Ar-H), 7.79 (d, *J*=8.8 Hz, 1H, Ar-H), 7.56 (d, *J*=8.8 Hz, 1H, Ar-H), 7.03 (d, *J*=8.8 Hz, 2H, Ar-H), 3.49 (m, 4H, $2CH_2$), 3.17 (s, 2H, NCH_2), 2.65 (m, 4H, $2CH_2$). ^{13}C NMR (DMSO-d_6, 100 MHz), δ ppm: 167.35, 159.78, 159.44 (C=O), 155.14 (coumarin C-3), 153.04 (Ar-C), 147.17 (coumarin C-4), 137.25, 134.23, 129.61, 129.34, 126.17 (2C), 120.12, 118.75, 113.08 (2C) (Ar-C), 59.48 (NCH_2), 52.52 ($2CH_2$), 46.73 ($2CH_2$). Anal. Calcd. For $C_{22}H_{20}ClN_5O_6$: C, 54.38; H, 4.15 and N, 14.41; found C, 54.27; H, 4.07 and N, 14.34.

6-Bromo-N'-{[4-(4-nitrophenyl)piperazin-1-yl]acetyl}-2-oxo-2H-chromene-3-carbohydrazide (**5c**): Yield: 3.82 g (72%). M.p. 222-223 °C, ^{1}H NMR (DMSO-d_6, 400 MHz), δ ppm: 10.44 (s, 2H, 2NH), 8.81 (s, 1H, coumarin-C_4-H), 8.26 (s, 1H, Ar-H), 8.04 (d, *J*=8.0 Hz, 2H, Ar-H), 7.90 (d, *J*=8.0 Hz, 1H, Ar-H), 7.50 (d, *J*=8.0 Hz, 1H, Ar-H), 7.03 (d, *J*=8.0 Hz, 2H, Ar-H), 3.49 (m, 4H, $2CH_2$), 3.17 (s, 2H, NCH_2), 2.65 (m, 4H, $2CH_2$). ^{13}C NMR (DMSO-d_6, 100 MHz), δ ppm: 167.35, 159.73, 159.44 (C=O), 155.14 (coumarin C-3), 153.45 (Ar-C), 147.11 (coumarin C-4), 137.25, 136.98, 132.62, 126.17 (2C), 120.61, 119.84, 118.99, 117.17, 113.08 (2C) (Ar-C), 59.49 (NCH_2), 52.52 ($2CH_2$), 46.73 ($2CH_2$). Anal. Calcd. For $C_{22}H_{20}BrN_5O_6$: C, 49.82; H, 3.80 and N, 13.21; found C, 49.73; H, 3.69 and N, 13.07.

7-(Diethylamino)-N'-{[4-(4-nitrophenyl)piperazin-1-yl]acetyl}-2-oxo-2H-chromene-3-carbohydrazide (**5d**): Yield: 3.97 g (76%). M.p. 200-201 °C, ^{1}H NMR (DMSO-d_6, 400 MHz), δ ppm: 10.34 (s, 2H, 2NH), 8.67 (s, 1H, coumarin-C_4-H), 8.23 (d, *J*=8.0 Hz, 1H, Ar-H), 8.04 (d, *J*=8.0 Hz, 1H, Ar-H), 7.69 (d, *J*=8.0 Hz, 1H, Ar-H), 7.62 (d, *J*=8.0 Hz, 1H, Ar-H), 7.03 (d, *J*=8.0 Hz, 1H, Ar-H), 6.81 (s, 1H, Ar-H), 6.63 (d, *J*=8.0 Hz, 1H, Ar-H), 3.50 (m, 8H, $4CH_2$), 3.17 (s, 2H, NCH_2), 2.71 (m, 4H, $2CH_2$), 1.14 (m, 6H, $2CH_3$). ^{13}C NMR (DMSO-d_6, 100 MHz), δ ppm: 167.47, 160.13, 159.87 (C=O), 154.84 (coumarin C-3), 152.41 (Ar-C), 148.01 (coumarin C-4), 137.21, 135.121, 130.02, 127.10, 124.15, 120.01, 119.87, 118.13, 117.10, 113.08, 96.73 (Ar-C), 59.49 (NCH_2), 52.52 ($2CH_2$), 44.93 ($2CH_2$), 44.85 ($2CH_2$), 12.76 ($2CH_3$). Anal. Calcd. For $C_{26}H_{30}N_6O_6$: C, 59.76; H, 5.79 and N, 16.08; found C, 59.68; H, 5.65 and N, 15.94.

Synthesis of compounds 6, 7 and 8

A solution of 2-[4-(4-nitrophenyl)piperazin-1-yl]acetohydrazide (**2**) (0.01 mol) and corresponding aldehyde in ethanol (15 mL, containing 0.5 mL of acetic acid) was refluxed for appropriate time (monitored by TLC, ethyl acetate/hexane, 3/1) in a round-bottomed flask. After the completion of the reaction, the mixture was cooled to room temperature. The product was precipitated by addition of water (10 mL). It was filtered off and recrystallized in ethanol.

2-[4-(4-Nitrophenyl)piperazin-1-yl]-N'-[3-oxo-1,3-dihydro-2H-indol-2-ylidene] acetohydrazide (**6**): Yield: 2.90 g (71%). M.p. 232-233 °C, ^{1}H NMR (DMSO-d_6, 400 MHz), δ ppm: 13.87 (s, 1H, NH $_{isatin}$), 11.20 (NH), 8.05 (d, *J*=8.8 Hz, 2H, Ar-H), 7.54 (d, *J*=7.2 Hz, 1H, Ar-H), 7.36-7.33 (m, 2H, Ar-H), 7.04 (d, *J*=8.8 Hz, 2H, Ar-H), 6.91 (d, *J*=7.2 Hz, 1H, Ar-H), 3.49 (m, 4H, $2CH_2$), 3.17 (s, 2H, NCH_2), 2.65 (m, 4H, $2CH_2$). ^{13}C NMR (DMSO-d_6, 100 MHz), δ ppm: 165.01, 162.66 (C=O), 155.18 (C=N), 144.42, 137.50, 132.11, 126.22 (2C), 123.02, 122.30, 121.30, 120.42, 115.72, 113.22 (2C), 112.42, 111.52 (Ar-C), 60.64 (NCH_2), 52.76 ($2CH_2$), 47.00 ($2CH_2$). Anal. Calcd. For $C_{20}H_{20}N_6O_4$: C, 58.82; H, 4.94 and N, 20.58; found C, 58.77; H, 4.85 and N, 20.47.

N'-[(3,5-Dichloro-2-hydroxyphenyl)methylidene]-2-[4-(4-nitrophenyl)piperazin-1-yl]acetohydrazide (**7**): Yield: 3.53 g (71%). M.p. 258-259 °C, ^{1}H NMR (DMSO-d_6, 400 MHz), δ ppm: 12.37 (s, 1H, OH), 11.90 (s, 1H, NH), 8.46+8.16 (s, 1H, N=CH, E/Z geometrical isomer, E/Z ratio75/25) 8.05 (d, *J*=8.4 Hz, 2H, Ar-H), 7.60 (s, 2H, Ar-H), 7.03 (d, *J*=8.4 Hz, 2H, Ar-H), 3.49 (m, 4H, $2CH_2$), 3.30+3.23 (s, 2H, NCH_2 , trans and cis amid conformer, cis/trans ratio 75/25), 2.63 (m, 4H, $2CH_2$). ^{13}C NMR (DMSO-d_6, 100 MHz), δ ppm: 168.20 (C=O), 155.11, 152.61 (Ar-C), 147.01 (N=CH), 137.34, 130.67, 128.76, 126.18 (2C), 123.23, 121.89, 121.17, 113.22 (2C) (Ar-C), 60.64 (NCH_2), 52.76 ($2CH_2$), 47.00 ($2CH_2$). Anal. Calcd. For $C_{19}H_{19}Cl_2N_5O_4$: C, 50.45; H, 4.23 and N, 15.48; found C, 50.36; H, 4.16 and N, 15.37.

N'-[Furan-2-ylmethylidene]-2-[4-(4-nitrophenyl)piperazin-1-yl]acetohydrazide (**8**): Yield: 2.85 g (80%). M.p. 211-212 °C, ^{1}H NMR (DMSO-d_6, 400 MHz), δ ppm: 11.25 (s, 1H, NH), 8.21+8.04 (s, 1H, N=CH, E/Z geometrical isomer, E/Z ratio 65/35) 8.02 (d, *J*=7.6 Hz, 2H, Ar-H), 7.82-7.77 (m, 1H, Ar-H), 7.02 (d, *J*=7.6 Hz, 2H, Ar-H), 6.85 (d, *J*=8.0 Hz, 1H, Ar-H), 6.60 (s, 1H, Ar-H), 3.50 (m, 4H, $2CH_2$), 3.45+3.23 (s, 2H, NCH_2 , trans and cis amid conformer, cis/trans ratio 65/35), 2.68 (m, 4H, $2CH_2$). ^{13}C NMR (DMSO-d_6, 100 MHz), δ ppm: 170.09 (Ar-C), 165.91 (C=O), 155.14, 149.83 (Ar-C), 147.57 (N=CH), 145.57, 137.54, 137.19, 133.52, 126.17 (2C), 113.79, 113.08 (2C), 112.51 (Ar-C), 60.58 (NCH_2), 52.68 ($2CH_2$), 46.48 ($2CH_2$). Anal. Calcd. For $C_{17}H_{19}N_5O_4$: C, 57.14; H, 5.36 and N, 19.60; found C, 57.06; H, 5.24 and N, 19.48.

Synthesis of compounds 9a, b

A solution of 2-[4-(4-nitrophenyl)piperazin-1-yl]acetohydrazide (**2**) (0.01 mol) and corresponding isothiocyanate in ethanol (15 mL) was taken in a round-bottomed flask. The mixture was refluxed for 3 hours. After the completion of the reaction (monitored by TLC, ethyl acetate/hexane, 4/1), the mixture was cooled to room temperature and a solid was appeared. This crude product was filtered off and washed with ethanol to obtain crude product.

N-Phenyl-2-{[4-(4-nitrophenyl)piperazin-1-yl]acetyl}hydrazinecarbothioamide (**9a**): Yield: 2.70 g (65%). M.p. 216-217 °C, ^{1}H NMR (DMSO-d_6, 400 MHz), δ ppm: 9.90 (s, 1H, NH), 9.56 (s, 2H, NH), 8.04 (d, *J*=8.4 Hz, 2H, Ar-H), 7.41 (m, 2H, Ar-H), 7.32 (t, *J*=7.6 Hz, 2H, Ar-H), 7.14 (m, 1H, Ar-H), 7.03 (d, *J*=7.6 Hz, 2H, Ar-H), 3.50 (m, 4H, $2CH_2$), 3.13 (s, 2H, NCH_2) 2.63 (m, 4H, $2CH_2$). ^{13}C NMR (DMSO-d_6, 100 MHz), δ ppm: 168.68 (C=O), 155.03, 149.55, 137.72, 134.50, 129.37 (2C), 128.75 (2C), 126.13 (2C), 113.11 (2C), 60.58 (NCH_2), 52.68 ($2CH_2$), 46.48 ($2CH_2$). Anal. Calcd. For $C_{19}H_{22}N_6O_3S$: C, 55.06; H, 5.35; S, 7.74 and N, 20.28; found C, 54.92; H, 5.19; S, 7.52 and N, 20.13.

N-[4-(4-Fluorophenyl)]-2-{[4-(4-nitrophenyl)piperazin-1-yl]acetyl}hydrazinecarbothioamide (**9b**): Yield: 3.07 g (71%). M.p. 218-219 °C, ^{1}H NMR (DMSO-d_6, 400 MHz), δ ppm: 9.87 (s, 1H, NH), 9.50 (s, 2H, NH), 8.04 (d, *J*=8.8 Hz, 2H, Ar-H), 7.28 (d, *J*=7.6 Hz, 2H, Ar-H), 7.12 (d, *J*=7.6 Hz, 2H, Ar-H), 7.03 (d, *J*=8.8 Hz, 2H, Ar-H), 3.49 (m, 4H, $2CH_2$), 3.11 (s, 2H, NCH_2) 2.63 (m, 4H, $2CH_2$). ^{13}C NMR (DMSO-d_6, 100 MHz), δ ppm: 168.68 (C=O), 155.13, 149.55, 137.24, 133.40, 131.17 (2C), 127.35 (2C), 122.11 (2C), 110.12 (2C), 60.49 (NCH_2), 53.71 ($2CH_2$), 45.43 ($2CH_2$). Anal. Calcd. For $C_{19}H_{21}FN_6O_3S$: C, 52.77; H, 4.89; S, 7.41 and N, 19.43; found C, 52.62; H, 4.76; S, 7.33 and N, 19.30.

Synthesis of compounds 10a, b

A solution of compounds **9a, b** (0.01 mol) in ethanol (20 mL) was refluxed with 2N NaOH (20 mL) for 6 hours. After the completion of the reaction (monitored by TLC, ethyl acetate/hexane, 4/1), the resulting solution was cooled to room temperature and acidified to pH 5-6 with 37% HCl. The crude product was filtered off, washed with water and recrystallized from ethanol/water (1:2) to afford compounds **10a, b**.

5-{[4-(4-Nitrophenyl)piperazin-1-yl]methyl}a-4-phenyl-4H-1,2,4-triazole-3-thiol (**10a**): Yield: 2.77 g (70%). M.p. 228-229 °C, ^{1}H NMR (DMSO-d_6, 400 MHz), δ ppm: 13.83 (s, 1H, SH), 8.01 (d, *J*=9.2 Hz, 2H, Ar-H), 7.53-7.44 (m, 5H, Ar-H), 6.95 (d, *J*=9.2 Hz, 2H, Ar-H), 3.39 (s, 2H, NCH_2), 3.24 (m, 4H, $2CH_2$) 2.33 (m, 4H, $2CH_2$). ^{13}C NMR (DMSO-d_6, 100 MHz), δ ppm: 168.68 (C=S), 155.03, 149.55 (C=N), 137.37, 134.49, 129.63, 129.38, 128.75, 126.13, 113.12, 51.86 ($2CH_2$), 46.64 ($2CH_2$), 40.59 (NCH_2). Anal. Calcd. For $C_{19}H_{20}N_6O_2S$: C, 57.56; H, 5.08; S, 8.09 and N, 21.20; found C, 57.39; H, 4.92; S, 7.91 and N, 21.06.

4-(4-Fluorophenyl)-5-{[4-(4-nitrophenyl)piperazin-1-yl]methyl}-4H-1,2,4-triazole-3-thiol (**10b**): Yield: 2.52 g (62%). M.p. 253-254 °C, ^{1}H NMR (DMSO-d_6, 400 MHz), δ ppm: 13.81 (s, 1H, SH), 8.23 (d, *J*=9.2 Hz, 2H, Ar-H), 7.32 (m, 4H, Ar-H), 6.95 (d, *J*=9.2 Hz, 2H, Ar-H), 3.37 (s, 2H, NCH_2), 3.28 (m, 4H, $2CH_2$) 2.36 (m, 4H, $2CH_2$). ^{13}C NMR (DMSO-d_6, 100 MHz), δ ppm: 168.71 (C=S), 155.03, 149.55 (C=N), 139.23, 137.35, 131.78, 129.87, 128.52, 126.14, 113.11, 51.93 ($2CH_2$), 46.65 ($2CH_2$), 40.59 (NCH_2). Anal. Calcd. For $C_{19}H_{19}FN_6O_2S$: C, 55.06; H, 4.62; S, 7.74 and N, 20.28; found C, 54.79; H, 4.48; S, 7.59 and N, 20.13.

CONCLUSION

This study reports the synthesis of some new hybrid molecules containing piperazine with some other pharmacophores in a single structure. According to the previous studies, it is obvious that hybrid molecules have higher biological activity than single molecules.[18, 19, 22-26] Therefore, these results can inspire researchers for the synthesis of new potential bioactive compounds.

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