Original Article

Design, synthesis and antitumor activity of new naproxen based 1,2,4-triazole-Schiff base derivatives

Nawaf I. Alsenani[1]

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Abstract
In the present work, new Naproxen based 1,2,4-triazole-Schiff base derivatives have been synthesized and screened for in vitro antitumor activity and in silico pharmacokinetic studies. The structure of the newly synthesized compounds (5–12) was elucidated by IR, NMR and mass spectrometry. All the compounds were tested against breast MCF-7, hepatocellular Huh-7 and lung A-549 cancer cell lines using MTT assay. Compound 7 was better in killing A549 cells with IC_{50} 3.71 µM (1.48 fold), compared with Doxorubicin (IC_{50} 5.50 µM). Also, compound **7** was found to be non toxic on MRC-5 normal cells as it depicts IC_{50} more than 500 µM. Besides, compound **12** also revealed promising activity with IC_{50} 6.94 and 3.33 µM against MCF-7 and Huh-7 respectively. The in silico studies displayed that the synthesized compounds favors the desired pharmacokinetic profile and drug likeness properties. It can be concluded that these new Naproxen based 1,2,4-triazole-Schiff base derivative (**7**) has the potential to be further investigated as lead molecule in the development of new chemotherapeutic agent.

Keywords Naproxen · 1,2,4-Triazole · Schiff base · Antitumor · Pharmacokinetics

1 Introduction

Cancer is the rapid proliferation of abnormal cells that has the tendency to invade other body parts resulting in high mortality rates [1, 2]. It is the leading cause of death globally accounting for nearly 10 million deaths in 2020 [3] and is expected to rise to 16.4 million by 2040 [4]. The most common cancers are breast, lung and colon and 30–50% of cancer mortality can be prevented through early detection, appropriate treatments and care of patients [5]. There has been a great advancement in cancer treatment which includes surgery, radiotherapy, chemotherapy and hormonal treatments [6, 7]. However due to dose toxicity, drug resistance to malignant tumours and selectivity of the current anticancer drugs [8], there is a need to develop effective chemotherapeutics to overcome these obstacles. Naproxen is a COX inhibitor and a potent NSAID. It has now been extensively studied for its anticancer potential as many of its derivatives inhibited proliferation in various cancers [9, 10]. Urea and propanamide derivatives of Naproxen inhibited cancer proliferation in colon cancer [11], Naproxen-1,3,4-oxaadiazole as EGFR inhibitors [12], Naproxen hydrazide-hydrazones as potent VEGFR-2 inhibitors [13], Naproxen-triazole hybrids as HDAc inhibitors [14] and provided protection in bladed cancer [15].

Heterocycles constitute a major portion in various therapeutic agents. 1,2,4-triazole is a five-member heterocycle with three nitrogen in the ring. This heterocycle motif is

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✉ Nawaf I. Alsenani, n.alsenani@bu.edu.sa | [1]Department of Chemistry, Faculty of Science, Albaha University, P.O. Box 1988, Al Baha, Kingdom of Saudi Arabia.

found in many molecular skeletons like Vorozole, Anastrozol and Letrozole as aromatase inhibitors [16], Fluconazole as antifungal agent [17], Estazolam and Alprazolam as tranquilizers [18] while Ribavirin as antiviral drug [19] and possess diverse pharmacological properties such as anticancer [20], antimicrobial [21], antiinflammatory [22], antiviral [23], analgesics [24] and antitubercular [25]. This motif can interact with different biological targets via hydrogen bonding, dipole–dipole interactions, Vander Waals forces and hydrophobic interactions [26]. On the other hand, Schiff bases are compounds containing azomethine group (–C = N–) which confers broad spectrum of biological activities like anticancer [27], anti-inflammatory [28], anticonvulsant [29], antimicrobial [30], antitubercular [31], and therefore attracted a great attention in medicinal chemistry. The electrophilic carbon and nucleophilic nitrogen provides excellent binding interactions with the biological targets thereby inhibiting target enzymes and DNA replication [32] and can be found in many drugs like Nifuroxide (antibiotic) [33], Thiacetazone (antitubercular) [34], Nitrofurantoin (antimicrobial) [35], so forth. On the basis of importance of 1,2,4-triazole and Schiff base, we combined these moieties with Naproxen and evaluated their antitumor activity against different cell lines. The present work describes the synthesis, antitumor and in silico pharmacokinetic studies of the new 1,2,4-triazole-Schiff base incorporated Naproxen derivatives (Fig. 1).

2 Results and discussion

2.1 Chemistry

The intermediates **2**–**4** were prepared using the reported method [12] with slight change. Naproxen **1** was reacted with methanol in presence of catalytic amount of concentrated sulphuric acid to yield compound **2** in pure form (91% yield). Then compound **2** was refluxed with hydrazine monohydrate in presence of methanol for 4 h to yield compound **3** (86% yield). The hydrazide **3** was dissolved in ethanolic KOH and added carbon disulfide dropwise at 0–5 ℃ followed by stirred at room temperature for 14 h yield potassium thiocarbamate salts, which was filtered. To this crude solid, hydrazine hydrate was added, and reflux for 12 h and then acidification with HCl solution yield main intermediate 4 (76% yield). Compound **4** was reacted with different aromatic aldehydes to yield new compounds **5**–**10** in 65–85% yield (Scheme 1) and reaction of compound 8 with different alkyl halide afforded compound **11**–**12** (Scheme 2).

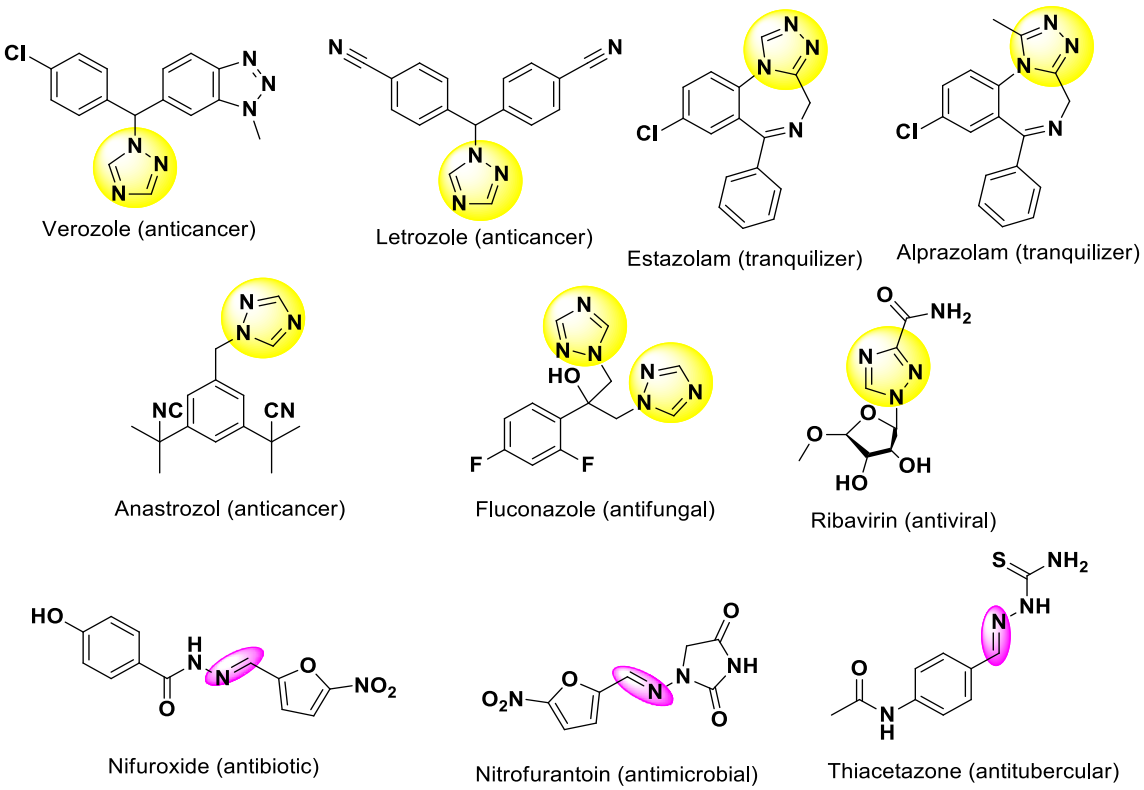
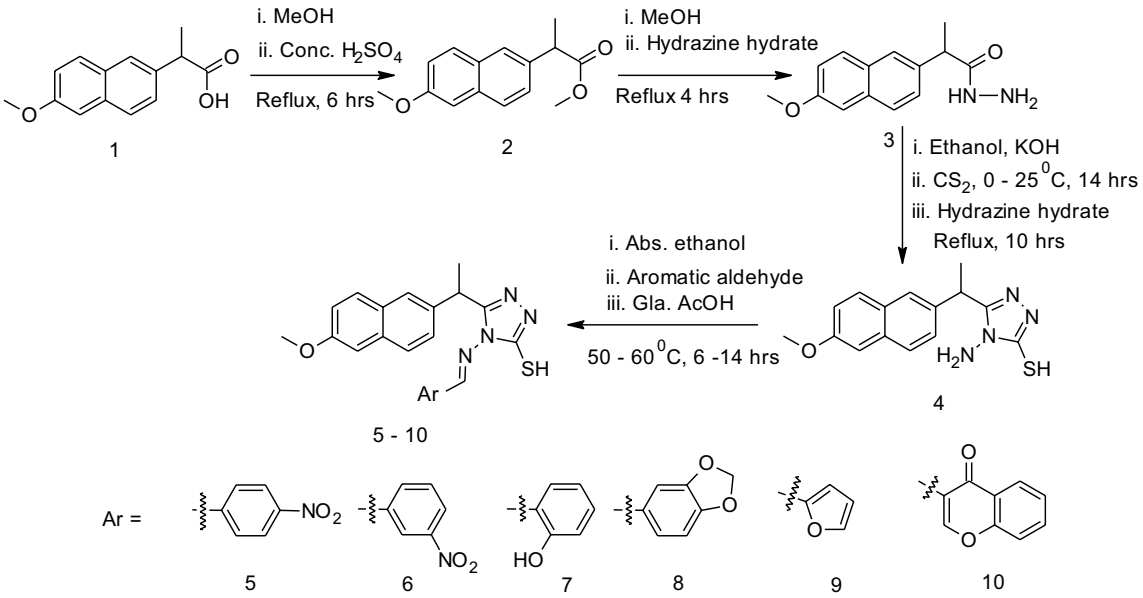


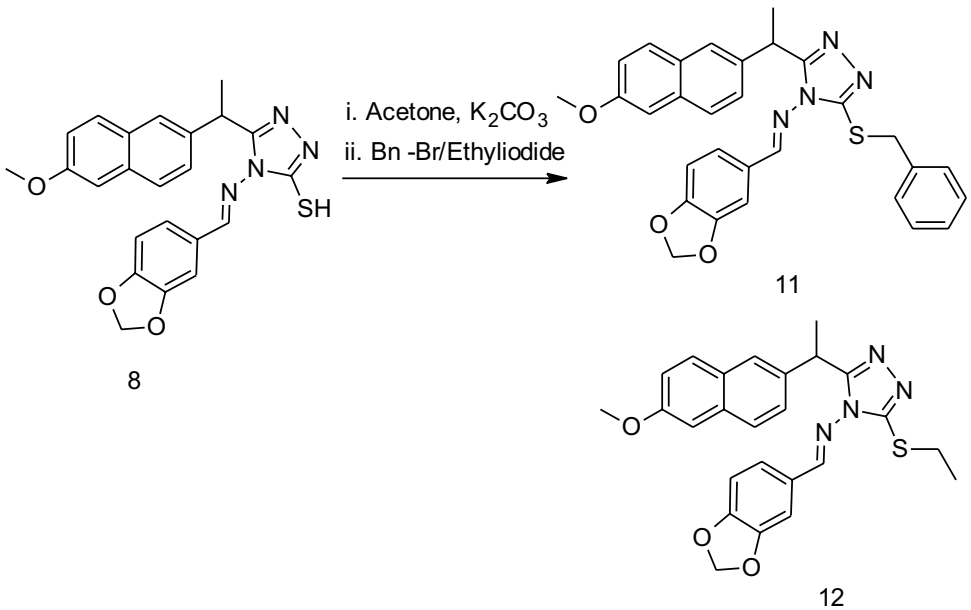
Fig. 1 Some of the important drugs containing 1,2,4-triazole and Schiff base scaffolds



Scheme 1 Synthesis of naproxen based 1,2,4-triazole bearing Schiff base (**5**–**10**)

All the newly synthesized compounds formation was confirmed by different analytical techniques such as FTIR, ^{1}H NMR, ^{13}C NMR and mass spectrometry. The ^{1}H NMR of compounds **5**–**7** and **9**–**10** displayed signals for azomethine protons merged with aromatic protons in the range 6.57–8.55 ppm, S–H proton signal in the range 9.93–10.48 ppm and aliphatic region showed peaks at 1.79–1.86 ppm, 4.43–4.65 ppm and 3.90–3.91 ppm ascribed to CH_3CH–, CH_3CH–$(Ar)_2$, and Ar–O–CH_3, respectively. These peaks were further supported by ^{13}C NMR which showed OCH_3, CH and CH_3 signals in upfield regions at 55.30–55.33 ppm, 36.32–36.89 ppm and 14.14–19.46 ppm respectively, HS–C = N of 1,2,4-triazole at 157.70–161.65 ppm, azomethine carbons at 155.09–159.72 ppm besides the aromatic carbons in the range 105.57–156.14 ppm. For instance, compound **7** formation was observed by the presence of two signals at 9.76 ppm and 9.93 ppm corresponds to –OH and S–H group, respectively whereas peaks at 1.81, 3.91, 4.43, and 9.93 were ascribed to CH_3, OCH_3, CH, and SH respectively. The azomethine and aromatic protons were found to be merged in the range 8.32–8.55 ppm. Piperonal based

Scheme 2 Synthesis of target molecules (**11**–**12**)



1,2,4-triazole-hydrazone derivative (**8**) displayed one additional signal at 6.08–6.10 ppm for Ar–O-CH_2 in ^{1}H NMR and at 102.13 ppm in ^{13}C NMR in addition to similar signals observed for compound **7**. Compound **10** showed a downfield signal in ^{13}C NMR spectra at 176.02 ppm for C = O confirming the presence of cromonyl group. Compounds **11** and **12** showed similar signals to compound **8** but both of them showed disappearance of –SH proton. Also, compound **11** exhibited appearance of additional S-CH_2 and five aromatic protons at 4.46 ppm and 7.21–7.38 ppm, occurred due to S-benzylation whereas compound **12** displayed a triplet at 1.42 ppm and broad singlet at 3.35 ppm integrating for three and two protons, respectively and signals at 14.62 ppm and 27.85 ppm correspond to -S-CH_2-CH_3 carbons in ^{1}H &^{13}C NMR, confirming alkylation at sulphur. Lastly, all the final compounds were confirmed by mass spectrometry displaying molecular ion peaks in the positive/negative mode.

2.2 In silico prediction

2.2.1 Physicochemical properties

Besides effectiveness, many molecules could not enter drug development due to poor bioavailability, absorption, water solubility and lipophilicity [6]. Therefore, the molecules must have good pharmacokinetic profile along with excellent pharmacological potential. There are certain criteria such as Lipinski rule of five which should be followed by the molecules in order to enter drug innovation [36]. The candidate must have molecular weight (M.W.) less than 500, lipophilicity (log P) below 5, hydrogen bond acceptor/donor must be below 10 and 5, respectively for easy transportation, excretion, diffusion and absorption. The synthesized final molecules were screened for in silico ADME predictions to have a look on their physiochemical and pharmacokinetic properties and the results are shown in Table 1. All the newly prepared compounds (**5–12**) were screened for their in-silico absorption, distribution, metabolism, excretion and toxicity (ADMET) study using swiss ADME and pKCSM data base tools [37]. From the results, it was observed that most of the compounds showed promising pharmacokinetics with molecular weight less than 500 except compound **11**, % absorption in the range 61.76–79.04, lipophilicity (log P) was found to be less than 5 in the range 3.06–4.90 and water solubility (log S) in the good range – 5.27 to 6.99. Also these compounds could not cross blood brain barrier and displayed desired skin permeability (log Kp) in the range – 5.05 to 5.82 for These data suggests that these Naproxen based 1,2,4-triazole-hydrazone derivatives follow Lipinski rule therefore possess desired pharmacokinetic and drug likeness properties as shown in Table 1.

2.3 In vitro antitumor activity

All the target molecules were evaluated for their antitumor activity against the three cancer cell lines MCF-7 (breast), Huh-7 (liver) and A-549 (lungs) by MTT method using the method of Mosmann [38]. Doxorubicin was used as standard drug which showed IC_{50} 1.85 µM, 1.40 µM and 5.50 µM against MCF-7, Huh-7 and A-549, respectively. From the results as shown in Figs. 2, 3 and 4, it was observed that the tested compounds showed variations in their activity from excellent to moderate in the range IC_{50} 4.72–46.80 µM, 1.91–28.10 µM and 3.71–56.63 µM against MCF-7, Huh-7 and A-549, respectively.

Among the tested derivatives, compound **7** was the most promising with IC_{50} 4.72, 1.91 and 3.71 µM, compared to the standard drug, Doxorubicin against MCF-7, Huh-7 and A-549 respectively. It can be seen that compound **7** was better in killing A549 cells with IC_{50} 3.71 µM (1.48 fold), compared with Doxorubicin (IC_{50} 5.50 µM). Also, compound **7** was found to be non toxic on MRC-5 normal cells as it depicts IC_{50} more than 500 µM. Besides, compound **12** also showed promising activity with IC_{50} 6.94 and 3.33 µM against MCF-7 and Huh-7 respectively. Compounds which were moderately toxic (IC_{50} < 20 µM) to

Table 1 ADMET studies of the target molecules **5**–**12**

Compounds	MW	LogP	nRB	nHBA	nHBD	Log S	% Abs	Log Kp	BBB
5	431	3.2	6	6	0	−5.77	61.76	−5.41	No
6	431	3.06	6	6	0	−5.77	61.76	−5.41	No
7	404	3.15	5	5	1	−5.58	70.59	−5.36	No
8	432	3.82	5	5	0	−5.43	74.38	−5.82	No
9	378	3.18	5	5	0	−5.27	73.03	−5.38	No
10	456	3.55	5	6	0	−6.04	67.14	−5.55	No
11	522	4.9	8	5	0	−6.99	79.04	−5.05	No
12	460	4.29	7	5	0	−5.91	79.04	−5.48	No

P octanol–water partition coefficient, *HBA* hydrogen bond acceptor, *HDB* hydrogen bond donor, *Log S* water solubility, *Log Kp* skin permeability, *%abs* absorption, *BBB* blood brain barrier

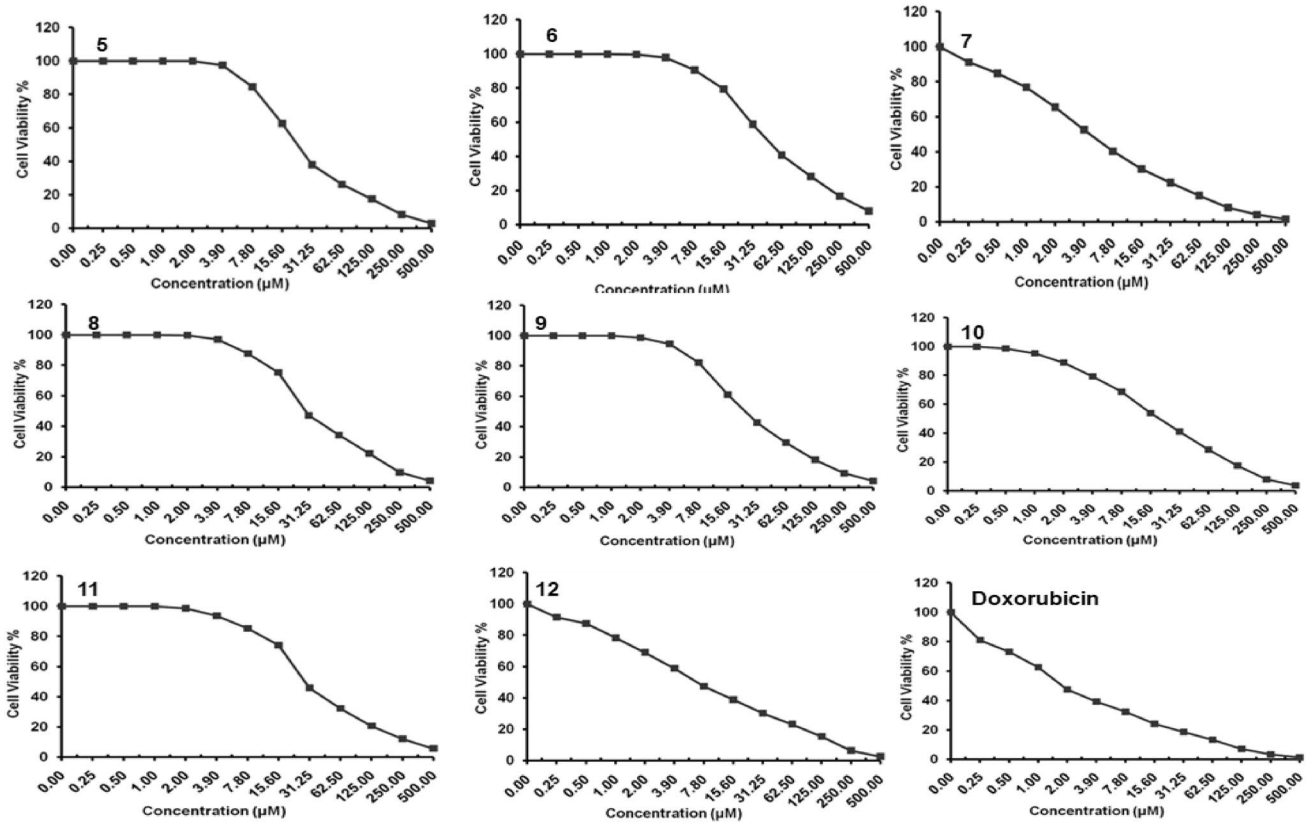


Fig. 2 Cell viability (%) of final compounds (**5**–**12**) against MCF-7 cells

the cancer cells were found to be **10** and **14** towards MCF-7; **9** and **10** against Huh-7; and compound **12** towards A-549 cells. Other compounds shown mild cytotoxicity with $IC_{50} < 50$ μM towards the tested cell lines except compound **9** which was less active against A-549 cells. The result of antitumor activity is shown in Table 2.

3 Material and methods

3.1 Chemistry

All the chemicals and reagent used for the synthesis of the target molecules were procured from Sigma Aldrich, Loba Chem and Across. The proposed structure of all the synthesized compounds was confirmed by different analytical techniques such as FT-IR (Thermo Scientific iS50), ^{1}H &^{13}C NMR (Bruker 850 MHz and 213 MHz respectively), Mass spectrometry (Thermo Scientific LCQ FLEET LCF10605), Elemental Analysis (LEECO Elementar Analyzer) while melting points were recorded on Stuart SMP40 machine which were uncorrected. The intermediate compounds 2–4 were prepared according to our previous method [12]. Dimethyl sulfoxide (DMSO), MTT and trypan blue dye was purchased from Sigma (St. Louis, Mo., USA). Fetal Bovine serum, RPMI-1640, HEPES buffer solution, L-glutamine, gentamycin and 0.25% Trypsin–EDTA were purchased from Lonza (Belgium).

General procedure for synthesis of compound 5–10

Compound **4** (0.001 mol) was taken in 100 mL round bottom flask and added 30 mL absolute ethanol, different aromatic aldehydes (0.001 mol) followed by addition of 3–5 drops of glacial acetic acid. The reactions mixture was stirred at 50–60 ℃ for 6–14 h. After completion of the reaction, the reactions mixture were concentrated to around 10 mL and poured onto the crushed ice, stirred to get solid precipitate. The products were filtered, washed with water and dried. The crude products were recrystallized from ethanol to get pure compounds with 68–86% yield.

5-[1-(6-methoxynaphthalen-2-yl)ethyl]-4-{[(4-nitrophenyl)methylidene]amino}-4H-1,2,4-triazole-3-thiol, 5

Yield: 72%; M.p: 166–168 ℃; FTIR (ν cm^{-1}): 2933, 1605, 1519, 1484, 1341, 1263, 1214, 1162, 1106, 1029, 850, 746; ^{1}H NMR ($CDCl_3$, 850 MHz) δ: 1.82 (d, $J = 8.5$ Hz, 3H, CH_3), 3.90 (s, 3H, Ar–O-CH_3), 4.61 (brd, s, 1H, Ar–CH), 7.07–7.13

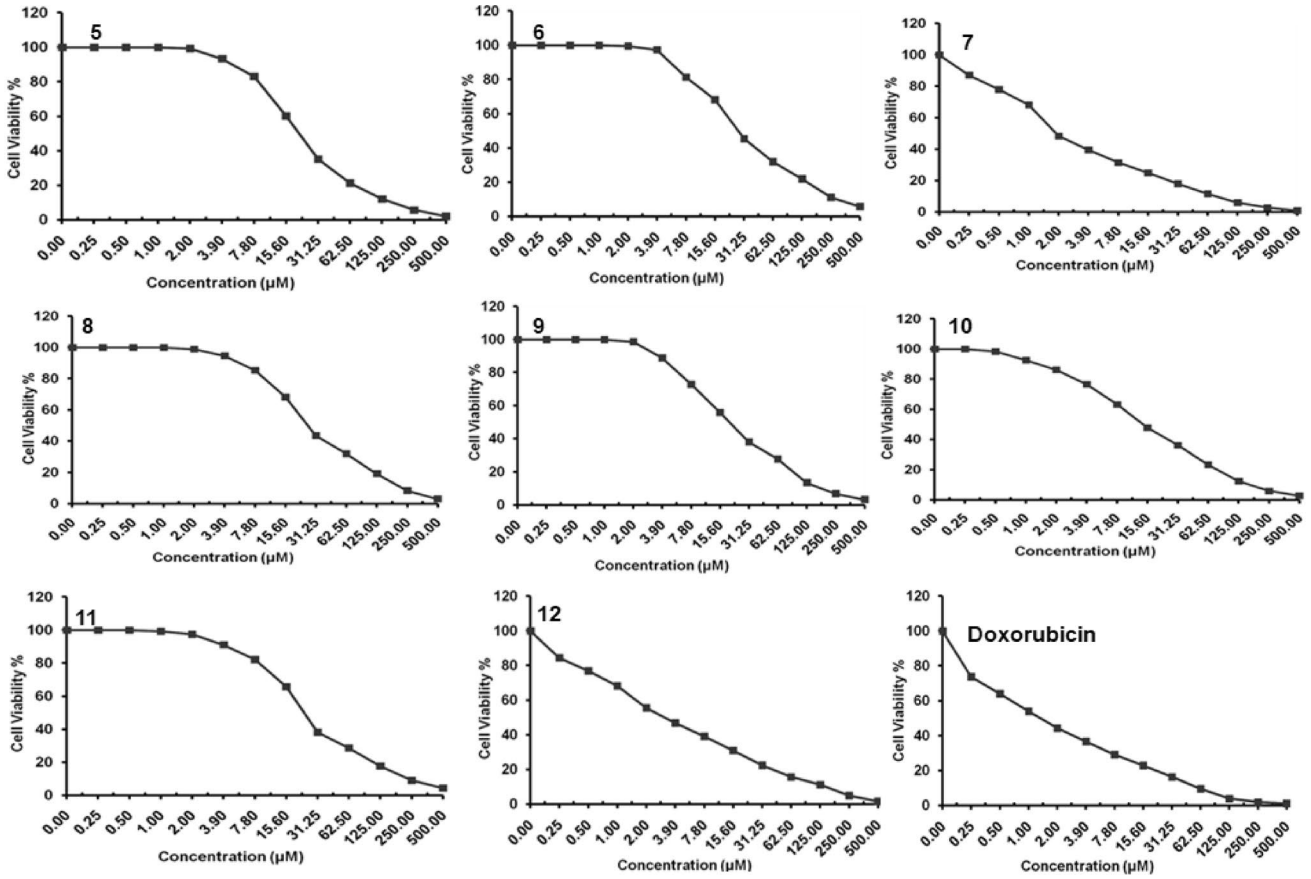


Fig. 3 Cell viability (%) of final compounds (**5**–**12**) against Huh-7 cells

(m, 3H, Ar–H), 7.35 (s, 1H, Ar–H), 7.62–7.86 (m, 5H, Ar–H), 8.25–8.27 (m, 2H, Ar–H), 10.48 (s, 1H, Ar-SH); ^{13}C NMR ($CDCl_3$, 213 MHz) δ: 14.14 (-CH_3), 36.81 (Ar–CH-CH_3), 55.33 (Ar–O-CH_3), 105.64, 119.36, 124.02, 124.33,126.64, 127.49, 127.63, 128.85, 129.03, 129.16, 130.51, 133.72, 135.84, 138.59, 149.68, 155.09, 157.82; ESI MS: *m/z* 432.08$[M+H]^+$,$C_{22}H_{19}N_5O_3S$ (Calcd): C, 60.96; H, 4.42; N, 16.16; S, 7.40. Obsd: C, 60.88, H, 4.44: N, 16.13; S, 7.38.

5-[1-(6-methoxynaphthalen-2-yl)ethyl]-4-{[(3-nitrophenyl)methylidene]amino}-4H-1,2,4-triazole-3-thiol, 6

Yield: 72%; M.p: 160–162 ℃; FTIR (ν cm^{-1}): 2931; 1605, 1506, 1342, 1263, 1162, 852,;^{1}H NMR ($CDCl_3$, 850 MHz) δ: 1.86 (d, *J* = 8.5 Hz, 3H, CH_3), 3.90 (s, 3H, Ar–O-CH_3), 4.51 (brd, s, 1H, Ar–CH), 7.04–7.12 (m, 4H, Ar–H), 7.72–7.81 (m, 4H, Ar–H), 8.21–8.26 (m, 2H, Ar–H), 8.51–8.55 (m, 1H, Ar–H), 10.15 (s, 1H, Ar-SH); ^{13}C NMR ($CDCl_3$, 213 MHz) δ: 18.15 (-CH_3), 36.89 (Ar–CH-CH_3), 55.30 (Ar–O-CH_3), 105.62, 119.34, 124.57, 125.67, 126.06, 127.58, 128.62, 128.86, 129.16, 130.39, 133.86, 134.61, 137.40, 148.81, 158.04, 160.34; ESI MS: *m/z* 432.08$[M+H]^+$, $C_{22}H_{19}N_5O_3S$ (Calcd): C, 60.96; H, 4.42; N, 16.16; S, 7.40. Obsd: C, 60.88, H, 4.44: N, 16.13; S, 7.38.

2-[(E)-({3-[1-(6-methoxynaphthalen-2-yl)ethyl]-5-sulfanyl-4H-1,2,4-triazol-4-yl}imino)methyl] phenol, 7

Yield: 81%; m.p, 196–198 ℃; FTIR (ν cm^{-1}):2934, 1605, 1519, 1484, 1341, 1264, 1230, 1172, 1106, 1030, 851, 746; ^{1}H NMR ($CDCl_3$, 850 MHz) δ: 1.81 (d, *J* = 8.5 Hz, 3H, CH_3), 3.91 (s, 3H, Ar–O-CH_3), 4.43 (brd, s, 1H, Ar–CH), 6.91–7.12 (m, 5H, Ar–H), 7.20–7.43 (m, 3H, Ar–H), 7.59–7.70 (m, 3H, Ar–H), 9.76 (s, 1H, Ar-OH), 9.93 (s, 1H, Ar-SH); ^{13}C NMR ($CDCl_3$, 213 MHz) δ: 19.78 (-CH_3), 37.12 (Ar–CH-CH_3), 55.31 (Ar–O-CH_3), 105.59, 115.85, 117.49, 117.65, 119.33, 119.87, 125.52, 127.84, 129.26, 133.56, 133.75, 137.03, 153.61, 157.85, 159.72, 161.65; ESI MS: *m/z* 403.08$[M-H]^+$; $C_{22}H_{20}N_4O_2S$ (Calcd): C, 65.33; H, 4.98; N, 13.85; S, 7.93. Obsd: C, 65.27, H, 3.32: N, 13.83; S, 7.91.

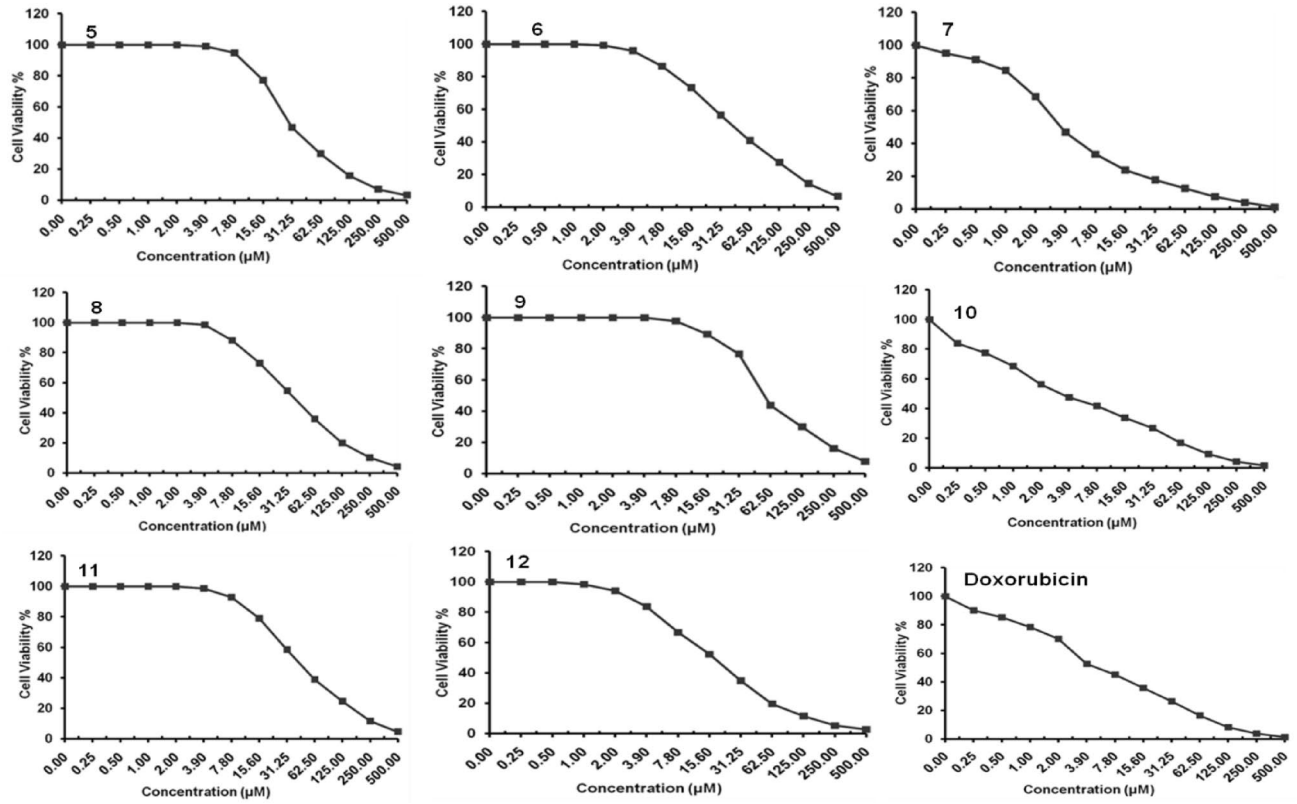


Fig. 4 Cell viability (%) of final compounds (**5**–**12**) against A-549 cells

Table 2 In vitro antitumor activity against MCF-7, Huh-7 and A-549 cells

Compounds	IC_{50} values (μM)		
	MCF-7	Huh-7	A-549
5	23.64 ± 1.46	22.00 ± 0.63	29.55 ± 0.91
6	46.80 ± 4.39	28.10 ± 1.61	44.24 ± 2.47
7	**4.72 ± 0.32**	**1.91 ± 0.06**	**3.71 ± 0.29**
8	29.55 ± 1.61	27.12 ± 2.07	39.20 ± 2.24
9	25.04 ± 2.55	20.68 ± 2.34	56.63 ± 2.53
10	20.25 ± 3.01	14.51 ± 0.91	44.45 ± 5.47
11	28.91 ± 0.79	24.38 ± 1.56	44.45 ± 5.47
12	6.94 ± 0.58	**3.33 ± 0.27**	17.61 ± 0.90
Doxorubicin	1.85 ± 0.12	1.40 ± 0.05	5.50 ± 0.70

IC_{50} are the mean ± S.D. of triplicate experiments; Doxorubicin: Standard reference drug

Bold values indicate the high results

E)-4-((benzo[d][1,3]dioxol-5-ylmethylene)amino)-5-(1-(6-methoxynaphthalen-2-yl)ethyl)-4H-1,2,4-triazole-3-thiol, 8

Yield: 86%; m.p.158–160 ℃; FTIR (ν cm^{-1}): 2934, 1605, 15 06, 1261, 1213, 1161, 1029, 845, 746; 1341, ^{1}H NMR ($CDCl_3$, 850 MHz) δ: 1.80 (d, J = 8.5 Hz, 3H, CH_3), 3.90–3.94 (m, 3H, Ar–O-CH_3, Ar–O-CH_2-O-Ar), 4.56–4.57 (m, 1H, Ar–CH), 6.08–6.10 (m, 2H, Ar–O-CH_2-O-Ar), 6.83 (d, J = 8.5 Hz,1H, Ar–H), 7.09–7.12 (m, 3H, Ar–H), 7.36–7.69 (m, 4H, Ar–H), 9.84 (s, 1H, Ar-SH); ^{13}C NMR ($CDCl_3$, 213 MHz) δ: 19.28 (-CH_3), 36.66 (Ar–CH-CH_3), 55.31 (Ar–O-CH_3), 102.13, 105.59, 106.95, 108.38, 119.13, 126.02, 126.13, 127.36, 128.73, 131.89, 133.70, 135.80, 148.73, 151.50, 153.14, 154.92, 157.71; ESI MS: *m/z* 431.08[M-H]$^+$, $C_{23}H_{20}N_4O_3S$ (Calcd): C, 63.87; H, 4.66; N, 12.95; S, 6.54. Obsd: C, 63.82; H, 4.62; N, 12.92; S, 6.52.

4-{[(E)-furan-2-ylmethylidene]amino}-5-[1-(6-methoxynaphthalen-2-yl)ethyl]-4H-1,2,4-triazole-3-thiol, 9

Yield: 68%; m.p. 220–222 ℃; FTIR (ν cm^{-1}): 3045, 2934, 1605, 1522, 1506, 1342, 1263, 1173, 1028, 881; ^{1}H NMR ($CDCl_3$, 850 MHz) δ: 1.79 (d, J = 8.5 Hz, 3H, CH_3), 3.91 (s, 3H, Ar–O-CH_3), 4.63–4.65 (m, 1H, Ar–CH), 6.57–6.60 (m, 1H, Ar–H), 6.96 (d, J = 8.50 Hz, 1H, Ar–H), 7.09–7.13 (m, 2H, Ar–H), 7.38 (s, 1H, Ar–H), 7.63–7.74 (m, 5H, Ar–H), 10.02 (s, 1H, Ar-SH); ^{13}C NMR ($CDCl_3$, 213 MHz) δ: 19.13 (-CH_3), 36.32 (Ar–CH-CH_3), 55.31 (Ar–O-CH_3), 105.57, 112.55, 118.56, 119.05, 126.16, 126.39, 127.25, 127.60, 128.81, 129.21, 133.69, 135.70, 146.77, 148.11, 149.13, 155.14, 157.70; ESI MS: *m/z* 377.08 [M-H]$^+$$C_{20}H_{18}N_4O_2S$ (Calcd): C, 63.47;

H, 4.79; N, 14.80; S, 8.47. Obsd: C, 63.52; H, 4.81; N, 14.82; S, 8.45.

(E)-3-(((3-mercapto-5-(1-(6-methoxynaphthalen-2-yl)ethyl)-4H-1,2,4-triazol-4-yl)imino)methyl)-4H-chromen-4-one, 10

Yield: 69%; m.p.220–222 ℃; FTIR (ν cm^{-1}):2933, 1604, 1562, 1485, 1344, 1262, 1213, 1163, 1030, 845. 750; ^{1}H NMR ($CDCl_3$, 850 MHz) δ: 1.79 (d, J = 8.5 Hz, 3H, CH_3), 3.90 (s, 3H, Ar–O-CH_3), 4.51–4.52 (m, 1H, Ar–CH), 7.09–7.12 (m, 1H, Ar–H), 7.30–7.79 (m, 8H, Ar–H), 8.25 (s, 1H, Ar–H), 8.32 (d, J = 8.5 Hz, 1H, Ar–H), 10.41 (s, 1H, Ar-SH); ^{13}C NMR ($CDCl_3$, 213 MHz) δ: 19.46 (-CH_3), 36.53 (Ar–CH-CH_3), 55.31 (Ar–O-CH_3), 105.64, 118.38, 118.63, 119.26, 120.33, 125.93, 126.24, 126.70, 127.49, 129.09, 134.48, 134.87, 156.10, 156.21, 160.77, 176.02; ESI MS: m/z 454.92 $[M-H]^+C_{25}H_{20}N_4O_3S$ (Calcd): C, 65.77; H, 4.42; N, 12.27; S, 7.02. Obsd: C, 65.71; H, 4.43; N, 12.25; S, 7.01.

General procedure for the synthesis of compound 11–12

Compound **8** (0.001 mol) was added into 100 mL round bottom flask followed by addition of dry acetone (50 mL) and potassium carbonate (0.0015 mol). To this reaction mixture, alkyl halides (0.001 mol) were added and the stirring was continued at 50–60 ℃ for 3–6 h. The reactions mixture were filtered when completed, filtrate were concentrated and poured over crushed ice (20 gm). The precipitated solids were filtered, washed with water and dried. The products were recrystallized in ethanol to get pure compounds with 74–80% yield.

(E)-N-(benzo[d][1,3]dioxol-5-ylmethylene)-3-(benzylthio)-5-(1-(6-methoxynaphthalen-2-yl) ethyl)-4H-1,2,4-triazol-4-amine, 11

Yield: 80%; m.p.260–262 ℃; FTIR (ν cm^{-1}): 2932, 1605, 1521, 1342, 1263, 1162, 1106, 1030, 851; ^{1}H NMR ($CDCl_3$, 850 MHz) δ: 1.91 (brs, 3H, CH_3), 3.91–3.92 (m, 3H, Ar–O-CH_3), 4.47–4.49 (m, 3H, Ar–CH and Ar-CH_2-), 6.09 (s, 2H, Ar–O-CH_2-O-Ar), 6.80 (t, J = 8.5 Hz, 2H, Ar–H), 7.08–7.09 (m, 2H, Ar–H), 7.21–7.38 (m, 5H, Ar–H), 7.55–7.68 (m, 4H, Ar–H); ^{13}C NMR ($CDCl_3$, 213 MHz) δ: 19.68 (-CH_3), 36.97 (Ar–CH-CH_3), 38.36 (Ar-CH_2-S-), 55.32 (Ar–O-CH_3), 102.07(Ar–O-CH_2-O-Ar), 105.53, 106.33, 108.40, 119.07, 125.59, 126.18, 127.45, 127.84, 128.72, 129.16, 133.63, 135.96, 148.60, 152.25, 157.70; ESI MS: m/z 523.18$[M+H]^+$; $C_{30}H_{26}N_4O_3S$ (Calcd): C, 68.95; H, 5.01; N, 10.72; S, 6.14. Obsd: C, 68.99; H, 5.03; N, 10.70; S, 6.11.

(E)-N-(benzo[d][1,3]dioxol-5-ylmethylene)-3-(ethylthio)-5-(1-(6-methoxynaphthalen-2-yl)ethyl)-4H-1,2,4-triazol-4-amine, 12

Yield: 74%; m.p. 144–146 ℃; FTIR (ν cm^{-1}): 2971, 2931, 1604, 1503, 1486, 1447, 1254, 1029, 924, 921, 853;^{1}H NMR ($CDCl_3$, 850 MHz) δ: 1.42 (t, J = 8.5 Hz, 3H, S-CH_2-CH_3), 1.93 (brd,s, 3H, CH_3), 3.35 (s, 2H, Ar-S-CH_2-CH_3), 3.91 (s, 3H, Ar–O-CH_3), 4.55 (brd, s, 1H, Ar–CH), 6.11 (s, 2H, Ar–O-CH_2), 6.82–6.93 (m, 2H, Ar–H), 7.08–7.67 (m, 7H, Ar–H), 7.99 (s, 1H, Ar–H); ^{13}C NMR ($CDCl_3$, 213 MHz) δ: 14.62 (-S-CH_2-CH_3), 19.57 (Ar-CH_3), 27.85 (S-CH_2-CH_3), 36.93 (Ar–CH-CH_3), 55.30 (Ar–O-CH_3), 102.18, 105.54, 106.34, 108.54, 119.20, 126.14, 126.31, 127.63, 128.82, 129.18, 133.73, 148.75, 152.60, 155.30, 157.79; ESI MS: m/z 461.08$[M+H]^+$; $C_{25}H_{24}N_4O_3S$ (Calcd): C, 65.20; H, 5.25; N, 12.17; S, 6.96. Obsd: C, 65.24; H, 5.27; N, 12.14; S, 6.98.

3.2 Antitumor activity

The antitumor activity of the newly synthesized compounds was tested against Breast MCF-7, Hepatocellular Huh-7 and lung A549 carcinomas using MTT protocol. The cell lines were obtained from the American Type Culture Collection (ATCC, Rockville, MD) and the activity was performed at Regional Center of Microbiology and Biotechnology, Al-Azhar University, Egypt. The positive reference drug used was Doxorubicin and the assay was performed according to published work [39]. The optical density was measured at 590 nm with the microplate reader (SunRise, TECAN, Inc, USA) to determine the number of viable cells and the percentage of viability was calculated as [(ODt/ODc)] × 100% where ODt is the mean optical density of wells treated with the tested sample and ODc is the mean optical density of untreated cells. The graph between surviving cells and drug concentration were plotted to get the survival curve of each tumor cell line after treatment with the specified compound. The IC_{50} for each compound was calculated from the dose response curve for each conc. using Graphpad Prism software (San Diego, CA. USA) [38].

4 Conclusion

In the present work, new Naproxen based 1,2,4-triazole-Schiff base derivatives have been synthesized and screened for in vitro antitumor activity and in silico pharmacokinetic studies. Compound **7** was found to be the most potent with IC_{50} 4.72, 1.91 and 3.71 µM, against

MCF-7, Huh-7 and A-549, respectively and was better in killing A549 cells than doxorubicin with 1.48 fold activity. The in silico studies displayed that the synthesized compounds favors the desired pharmacokinetic profile and drug likeness properties. It can be concluded that these new Naproxen based 1,2,4-triazole-Schiff base derivative (**7**) could be further investigated as lead molecule in the development of new chemotherapeutic agents.

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Availability of data and materials All dataset is available upon reasonable request.

Declarations

Conflict of interest There is no conflict of interest.

Did your research involve plants/animals? It was done in vitro.

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