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Design, synthesis and biological evaluation of substituted 2-amino-1,3-thiazine derivatives as antituberculosis and anti-cancer agents

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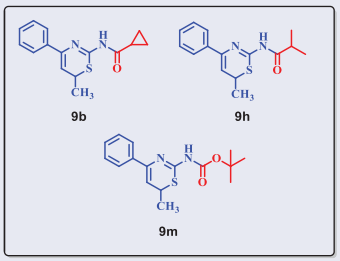
ABSTRACT

A series of substituted 2-amino-1,3-thiazines were synthesized as amides (**9a–9i**), carbamates (**9j–9m**), sulfonamides (**9n–9o**) and urea derivatives (**9p–9q**) by treating the compound **7** with acid chlorides (**8a–8i**), chloroformates (**8j–8m**), sulfonyl chlorides (**8n–8o**) and isocyanates (**8p–8q**) respectively. The synthesized compounds (**9a–9q**) were screened for *antituberculosis* activity against *Mycobacterium tuberculosis* $H_{37}Rv$ ATCC 27294 and the results show that some of these derivatives possess good activity against *Mycobacterium tuberculosis* $H_{37}Rv$ ATCC 27294. A few also display promising cytotoxic activity against human breast cancer MCF-7 and human esophageal cancer EC-9706 cell lines. Regarding both biological profiles **9b, 9m** and **9h** are the most active for anti-cancer, anti-TB activity.

GRAPHICAL ABSTRACT



Compound	Anti-TB MIC	Anti-cancer(IC50)	
		MCF-7	EC-9706
9b	1.26 µg/mL	1.73 µM	6.12 µM
9h	1.56 µg/mL	5.48 µM	9.12 µM
9m	3.12 µg/mL	2.26 µM	5.18 µM

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KEYWORDS
2-amino-,1,3-thiazine; *Mycobacterium tuberculosis* H37Rv ATCC 27294; human breast cancer MCF-7; human esophageal cancer EC-9706; cytotoxic activity; antituberculosis agent; anticancer agent

Introduction

Nitrogen and Sulfur containing heterocycles like thiazines, thiazoles are certainly one of the most imperative targets in organic chemistry and extensively distributed in natural products, biologically active compounds and pharmaceutical agents. 1,3-thiazine

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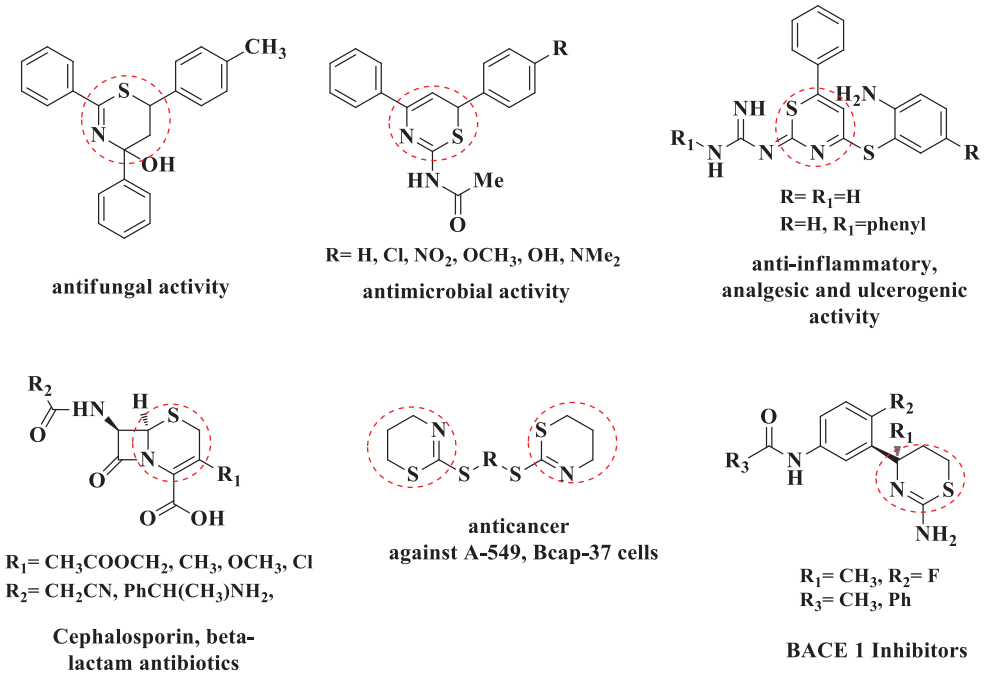


Figure 1. Some of the potent biologically active compounds possessing thiazine core.

derivatives have been found as versatile pharmacophores to be associated with various biological and pharmacological properties such as anti-cancer,[1] BACE inhibitors,[2] antimicrobial,[3] anti-diabetic,[4] antihistamine,[5] antibacterial,[6] anti-convulsant,[7] vasopressin receptor antagonistic,[8] potassium channel-opening agents,[9] antioxidant,[10] anti-tumor[11] and anti-inflammatory,[12] antituberculosis,[13] insecticidal[14] nitric-oxide synthase inhibitor,[15] smooth muscle relaxants[16] antimycobacterial[17] and myocardial calcium channel modulators,[18] (Figure 1).

Haider and coworkers[19] utilized 1,3-thiazine derivatives for antimicrobial activity. Sawant and coworkers[20] synthesized *N*-acetyl-1,3-thiazines and evaluated their efficacy as antimicrobial agents. Ali and coworkers[21] have synthesized a series of 1,3-thiazines incorporating acridine moieties and evaluated their antimicrobial activity. Further, Dabholkar and coworkers[22] have synthesized 1,3-thiazine derivatives for anti-inflammatory, analgesic and ulcerogenic activity. Due to the significance of 1,3-thiazine derivatives, many researchers are pursuing these molecules to obtain enhanced activity against various cell lines. As a part of our research in medicinal chemistry,[23] we focused on novel 2-amino-1,3-thiazine derivatives with *antituberculosis* activity against M. tuberculosis H_{37}RvATCC 27294 and anti-cancer activity against MCF-7, EC-9706 cell lines.

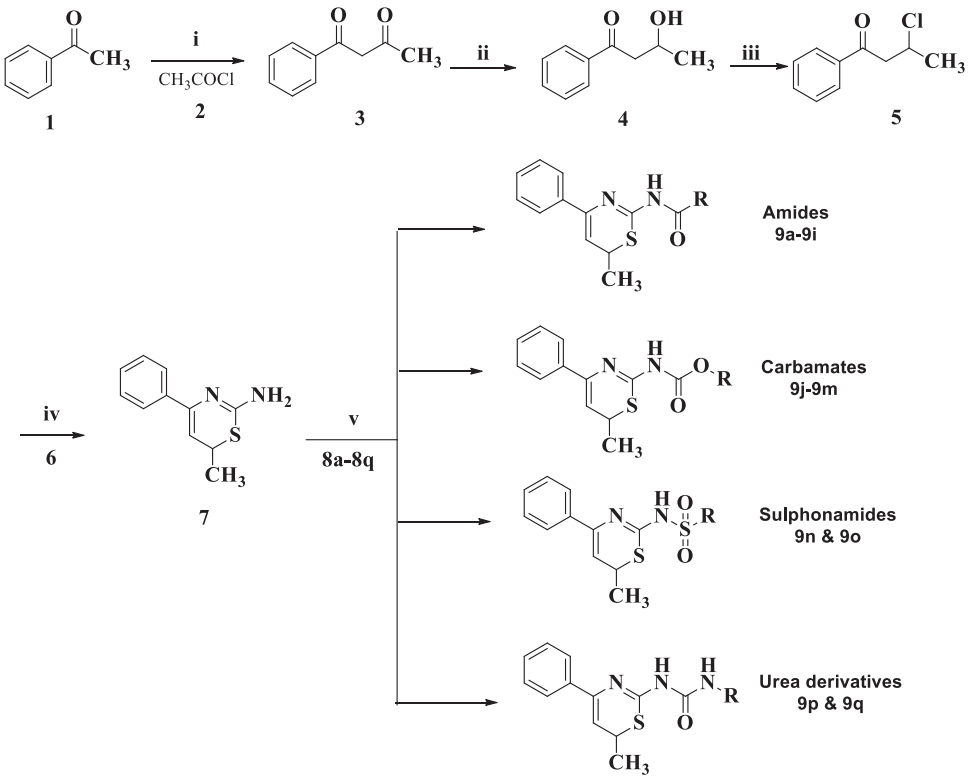
Tuberculosis (TB) is acontagious disease caused by *Mycobacterium tuberculosis* (Mtb)and affects mainly on the lungs and other organs of the body. According to WHO analysis, 50 million peoples are suffering from this disease and the number has been increasing in developing countries including India.[24] WHO estimating that 9 million new cases are increasing every year.[25,26] Based on these reports, researchers are

focusing more on development of new drug molecules as resistant strains of *Mycobacterium tuberculosis*. This underscores the need for continuous developments of novel and efficient antimicrobial molecules against drug resistant TB.[27,28]

Results and discussion

Synthesis

The preparation of substituted *N*-(6-methyl-4-phenyl-6*H*-1,3-thiazin-2-yl) compounds **9a–9q** have been carried out by the synthetic sequence illustrated in Scheme 1. By using the protocol (see supporting information) we have synthesized the 3-hydroxy-1-phenyl-1-butanone[29] **4** in 85% yield. Chlorination of **4** in presence of $SOCl_2$ and a catalytic amount of DMF in DCM at room temperature for 3 h resulted in the formation of 3-chloro-1-phenylbutan-1-one (**5**) in 89% yield. Cyclization of **5** with thiourea **6** in ethanol at reflux temperature for 8 h gave 6-methyl-4-phenyl-6*H*-1,3-thiazin-2-amine (**7**) in 84%



Scheme 1. Synthesis of 1,3-thiazine derivatives (**9a–9q**). Reagents and conditions: (i) LiHMDS, Toluene, 0 °C, 1 h; (ii) LiHMDS, $LiAlH_4$, THF, 0 °C, 1 h; (iii) $SOCl_2$, CH_2Cl_2, DMF, RT, 3 h; (iv) thiourea (**6**), ethanol, 75 °C, 8 h; (v) Compounds **8a–8s**, DIPEA, CH_2Cl_2, RT, 2 h. **8a:**pivaloyl chloride; **8b:**cyclopropanecarbonyl chloride; **8c:**cyclopentanecarbonyl chloride; **8d:**cyclohexanecarbonyl chloride; **8e:**isobutyryl chloride; **8f:** 2,2-dimethyl butyryl chloride; **8g:**propionyl chloride; **8h:**butyryl chloride; **8i:**benzoyl chloride; **8j:**methyl chloroformate; **8k:**ethyl chloroformate; **8l:***iso*-propyl chloroformate; **8m:***tert*-butylchloroformate; **8n:**methanesulfonyl chloride; **8o:**4-(trifluoromethoxy)benzene-1-sulfonyl chloride; **8p:**2-F-phenyl isocynate; **8q:**2-Cl-phenyl isocyanate.

yield. Coupling of amine **7** with various acid chlorides **8a–8i**, chloroformates **8j–8m**, sulfonyl chlorides **8n–8o** and phenyl isocyanates, **8p–8q** in presence of DIPEA in DCM at room temperature for 2 h resulted in the formation of thiazine derivatives **9a–9q.**

Biological studies

To explore the structural activity relationship (SAR) of synthesized compounds, the compounds (**9a–9q)** were examined for their antituberculosis activity and the minimum inhibitory concentration (MIC) was determined (Table 1). Most of the derivatives have shown potential tuberculosis efficacy with the MIC values <5 μg/mL. The compounds have been classified into four categories based on the structural variation at amide linkage. The four categories include aliphatic/aromatic amides, carbamates, sulfonamides and urea derivatives respectively. The results were compared with unmodified thiazine compound **7** which has shown MIC value more than 25 μg/mL These results indicate that the first category of the compounds **9a–9i** possessing aliphatic and aromatic amides have shown moderate to good activity.

Interestingly the compound **9b** with cyclopropyl amide linkage was exhibited an impressive activity (MIC = 1.26 μg/mL), whereas the compounds in the same category **9h** and **9f** have shown the MIC values 1.56 μg/mL and 6.25 μg/mL respectively. The compound **9i** with phenyl amide has shown high potential activity with MIC value 0.78 μg/mL. The second major class of compounds with carbamate linkages also exhibited

Table 1. Anti tuberculosis, anti-cancer activity results of 1,3-thiazine derivatives **9a–9q**.

S.No	Compounds (R)	Anti-TB MIC in μg /mL	Anti-cancer Cytotoxicity inhibition (IC_{50})[a]	
			MCF-7	EC-9706
1	7	>25	15.42	>100
Amides				
2	**9a** (*t*-butyl)	6.25	22.46	18.46
3	**9b** (cyclopropyl)	1.26	1.73	6.12
4	**9c** (cyclopentyl)	>25	24.19	23.45
5	**9d** (cyclohexyl)	>25	10.55	12.94
6	**9e** (isopropyl)	25	20.50	26.18
7	**9f** (1-(2-methyl)butyl)	6.25	>100	3.81
8	**9g** (ethyl)	25	34.18	20.48
9	**9h** (propyl)	1.56	5.48	9.12
10	**9i** (phenyl)	0.78	16.48	20.92
Carbamates				
11	**9j** (methyl)	6.25	19.64	30.27
12	**9k** (ethyl)	6.25	5.83	>100
13	**9l** (isopropyl)	>25	>100	7.26
14	**9m** (*t*-butyl)	3.12	2.26	5.18
Sulfonamides				
15	**9n** (methyl)	>25	3.68	10.55
16	**9o** (4-OCF_3 phenyl)	6.25	7.69	>100
Urea derivatives				
17	**9p** (2-F phenyl)	3.12	8.60	2.61
18	**9q** (2-Cl phenyl)	6.25	>100	7.26
19	Isoniazid	0.72	ND	ND
20	Rifampicin	0.24	ND	ND
21	Ethambutol	7.64	ND	ND
22	Cisplatin	ND	4.12	7.10

[a]Inhibitory activity was assayed by exposure for 72 h substances and expressed as concentration required to inhibit tumor cell proliferation by 50% (IC_{50}). ND means not determined.

high potential activity. The compound **9 m** with *tert*-butyl group showed remarkable activity with MIC (3.12 μg/mL). The compounds **9j** and **9k** with methyl and ethyl groups respectively exhibited comparable activity with MIC 6.25 μg/mL, whereas the compound **9i** with isopropyl group has shown the lowest activity. The third category of compounds with sulfonamide linkages have shown diverse activity like **9o** with *p*-trifluoromethyl phenyl sulfonamide showed remarkable activity (MIC = 6.25 μg/mL) while **9n** with simple methyl group has shown least potential (MIC > 25 μg/mL). The fourth category comprising urea derivatives exhibited pronounced activity with compound **9p** having MIC 3.12 μg/mL and compound **9q** havingMIC 6.25 μg/mL.

In the present study, we evaluated the 1,3-thiazine derivatives (**9a–9q**) as anti-cancer agents against MCF-7 and EC-9706 cell lines (Table 1). With regard to selectivity against individual cell lines, many of the compounds showed effectiveness against human breast cancer MCF-7 and human esophageal cancer EC-9706 cell lines with IC_{50} values ranging from 1.73 to 34.18 μM and 2.61 to 30.27 μM respectively in comparison to cisplatin (4.12 and 7.10 μM) (Table 1). Regarding MCF-7 human breast cancer cell line, a higher potency was observed with compounds **9b, 9m,** and **9n** with IC_{50} concentrations of 1.73, 2.26, and 3.68 μM comparative to cisplatin IC_{50} (4.12 μM). On the other hand compounds **9h, 9k, 9o,** and **9p** showed a slightly higher cytotoxic activity compared to standard cisplatin (i.e. **9h** = 5.48**, 9k** = 5.83**, 9o** = 7.69 and **9p** = 8.60). For EC-9706 human esophageal cancer cell line, the compounds **9p, 9f,** and **9b** showed the highest activity with IC_{50} values of 2.61, 3.81 and 6.12 μM respectively comparative to reference drug cisplatin (7.10 μM). Furthermore the compounds **9h, 9m** and **9q** exhibit moderate activity (9.12, 5.18 and 7.26 μM respectively) with compared to reference drug cisplatin.

Some structure-activity relationships could be observed, mainly related to the influence of different substituents at 2^{nd} position of thiazine core moiety R = cyclopropyl, *tert*-butyl, methyl, fluorobenzene, 1-(2-methyl)butyl. From the recorded IC_{50} values of these compounds **9a–9q** it was observed that different substituent's on thiazines exemplified varying degrees of inhibition against the two cancer cell lines. The comparison of the activities of compounds, suggesting that the introduction of electron-donating groups like methyl or *tert*-butyl contributed to anti-cancer activities whereas, the electron-withdrawing group like fluorine showed a decrease in the antitumor properties. Regarding both biological profiles **9b, 9m,** and **9h** are the most active for anti-cancer, anti-TB activity.

Experimental

Materials and methods

All raw material and reagents were procured Aldrich chemicals, AVRA fine chem and spectrochem. Readily available TLC silica gel plates (Kieselgel 60 F254, Merck) were used to monitoring reactions. All synthesized molecules were purified by coloumn chromatography using 60-120 silica gel (particle size 60–120 mesh, Merck). IR (KBr) data was recorded on a Perkin–Elmer 400 FTIR spectrometer (υ_{max} in cm^{-1}). ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker DRX-400 (400 MHz FT NMR) or Varian Mercury 500 MHz spectrometer in $CDCl_3$/DMSO-d_6.

General procedure for the synthesis of 9a–9q

To a solution of 6-methyl-4-phenyl-2*H*-1,3-thiazin-2-amine **7** (1.4 mmol) in 2–3 mL CH_2Cl_2 was added DIPEA at 0 °C maintained over 10 min, then acid chlorides **8a–8q** (1.76 mmol) was added and stirred the reaction mixture for 2 h at room temperature. After completion of reaction on TLC, the reaction mixture was quenched with cold ice water. Diluted with ethyl acetate, washed with aqueous bicarbonate solution, followed by brine solution. The organic layer was dried over Na_2SO_4 then concentrated and purified by column chromatography on silica gel (10% ethyl acetate in pet ether) to afford pure compounds.

N-(6-Methyl-4-phenyl-6H-1,3-thiazin-2-yl)cyclopropane carboxamide (9b)

The compound **9b** was prepared according to general procedure by utilizing cyclopropane carbonyl chloride **8b**. Pale brown solid; Yield: 91%; M.P: 130–133 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.56 (dd, J = 1.7, 7.9 Hz, 2H), 7.40–7.29 (m, 3H), 5.55 (d, J = 5.8 Hz, 1H), 3.82-377 (m, 1H), 1.88–1.74 (m, 1H), 1.47 (d, J = 7.0 Hz, 3H), 1.09 (td, J = 3.3, 4.6 Hz, 2H), 0.88 (dd, J = 3.0, 8.0 Hz, 2H); 13C NMR (125 MHz, $CDCl_3$) δ ppm: 189.82 (CO), 163.02 (C2), 143.44 (C6), 135.81 (ArC), 135.46 (ArC), 129.95 (ArC), 129.57 (ArC), 129.42 (ArC), 128.72 (ArC), 123.06 (C5), 30.39 (C4), 29.72 (CH_3), 21.72 (CH_2), 11.04 (CH_2). IR (KBr, cm^{-1}): 3254 (NH str), 3002, 2980, 2915 (CH_2 str), 1661 (CO str), 1616, 1598, 1552 (Ar–C=C str), 1229 (C–S–C str); HRMS (ESI): calcd for $C_{15}H_{17}N_2OS$ $(M + H)^+$: 273.102 found 273.104.

N-(6-Methyl-4-phenyl-6H-1,3-thiazin-2-yl)butyramide (9h)

The compound **9h** was prepared according to general procedure by utilizing butyryl chloride **8h**. Brown solid; Yield: 83%; 140–142 °C ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.62–7.59 (m, 2H), 7.39–7.28 (m, 3H), 5.58 (d, J = 5.8 Hz, 1H), 3.86–3.70 (m, 1H), 2.49 (q, J = 7.5 Hz, 2H), 1.46 (d, J = 6.9 Hz, 3H), 1.20 (t, J = 7.5 Hz, 3H); 13C NMR (100 MHz, $CDCl_3$) δ ppm: 173.04 (CO), 169.00 (C2), 153.16 (C6), 142.34 (ArC), 142.12 (ArC), 130.17 (ArC), 129.60 (ArC), 128.09 (ArC), 124.98 (ArC), 124.72 (C5), 60.07 ($\underline{C}H_2$), 42.17 (C4), 28.95 ($\underline{C}H_3$), 22.02 ($\underline{C}H_2$), 21.92 ($\underline{C}H_3$). IR (KBr, cm^{-1}): 3434 (NH str), 2962 (CH_3 str), 2925 (CH_3 str), 1698 (CO str), 1557 (Ar–C=C str), 1259 (C=N str), 1152 (C–S–C str); HRMS (ESI): calcd for $C_{16}H_{21}N_2OS$ $(M + H)^+$: 275.121 found 275.082.

Tert-butyl-6-methyl-4-phenyl-6H-1,3-thiazin-2-ylcarbamate (9m)

The compound **9m** was prepared according to general procedure by utilizing tertbutyl chloro formate **8m**. Brown solid; Yield: 90%; 127–128 °C ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.53–7.48 (m, 2H), 7.42–7.39 (m, 3H), 5.48 (d, J = 5.6 Hz, 1H), 3.82–3.77 (m, 1H), 1.54–1.42 (m, 12H); 13C NMR (100 MHz, $CDCl_3$) δ ppm: 166.97 (C2), 159.76 (C6), 151.10 (ArC), 131.48 (ArC), 129.19 (ArC), 127.49 (ArC), 126.25 (ArC), 124.89 (ArC), 121.78 (ArC), 119.89 (C5), 50.40 ($O\underline{C}(CH_3)_3$), 30.18 ($\underline{C}H$), 26.78 ($\underline{C}H_3)_3$, 24.18 ($\underline{C}H_3$), 21.07 ($\underline{C}H_3$); IR (KBr, cm^{-1}): 3436 (NH str), 3052 (=CH str), 2975 (CH_3 str), 2924

(CH str), 1731 (CO str), 1617, 1567, 1481 (Ar–C=C str), 1368 (=CN str), 1239 (C–S–C str), 755. HRMS (ESI): calcd for $C_{15}H_{19}N_2O_2S$ $(M + H)^+$: 305.712 found 306.715.

Conclusion

In conclusion, we have designed and synthesized a series of substituted N-(6-methyl-4-phenyl-2H-1,3-thiazin-2-yl) hybrids **9a–9q**. All the newly synthesized compounds were characterized by ^{1}H NMR, ^{13}C NMR, mass, HRMS and IR spectral data. The *in vitro* overall results indicated that the compounds **9b, 9h, 9i, 9m** and **9p** showed excellent anti-tuberculosis activity with MIC value 1.26 µg/mL, 1.56 µg/mL, 0.78 µg/mL, 3.12 µg/mL, and 3.12 µg/mL respectively compared to standard Ethambutol. All the synthesized compounds were screened for cytotoxic activity against cancer cell lines MCF-7, EC-9706 by MTT colorimetric assay. The compounds **9b, 9h, 9k, 9m, 9n, 9o, and 9p** displayed promising cytotoxic activity against MCF-7 cell lines with IC_{50} of 1.73 µM, 5.48 µM, 5.83 µM, 2.26 µM, 3.68 µM, 7.69 and 8.60 respectively. The compounds **9b, 9f, 9h, 9l, 9m, 9p** and **9q** displayed good cytotoxic activity against EC-9706 cell lines with IC_{50} of 6.12 µM, 3.81 µM, 9.12 µM, 7.26 µM, 5.18 µM, 2.61 µM and 7.26 µM respectively. Cisplatin was taken as standard and it showed the cytotoxicity against MCF-7 and EC-9706 cell lines with the IC_{50} value of 4.12 µM and 7.10 µM respectively.

Supplementary information (SI)

Full experimental detail, 1 H and 13 C NMR spectra. This material can be found via the "Supplementary Content" section.

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