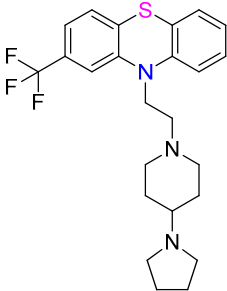
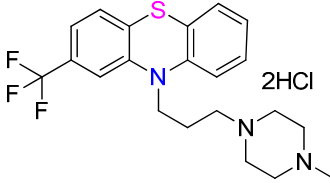
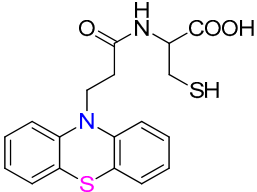
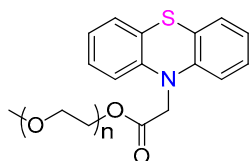


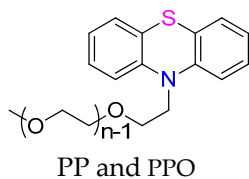
Table S1. The parameter values of anticancer activity of selected phenothiazines.

Compound	Cells/Tissues	IC ₅₀ ($\mu\text{M} \pm \text{SD}$ or $\mu\text{g/mL}$)	Mechanisms	Effective	Ref.
 10-(2-(4-(pyrrolidin-1-yl)piperidin-1-yl)ethyl)-2-(trifluoromethyl)-10H-phenothiazine	U87MG GBL28 NSC	2.3* 2.2 3.2	Ca ²⁺ ↑	82% 85% 45%	89
 10-(3-(4-methylpiperazin-1-yl)propyl)-2-(trifluoromethyl)-10H-phenothiazine	U87MG GBL28 NSC	*TFP 9.9 10.2 10.1		82% 85% 21%	
 2-(3-(10H-phenothiazin-10-yl)propanamido)-3-mercaptopropanoic acid		4.7 $\pm$ 0.5	FTase↓	92%	90



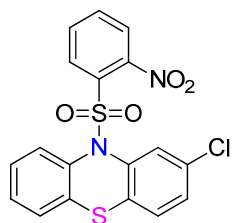
HepG2

cytotoxic effect ↑ tumour growth ↓



HeLa
MeWo

91



U251
U87

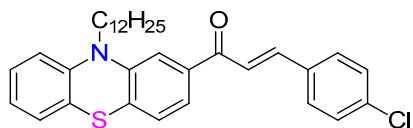
5.12
9.29

LC3-II↑

G1 cell cycle
arrest↑,
cell viability↓

92

2-chloro-10-((2-nitrophenyl)sulfonyl)-10H-phenothiazine

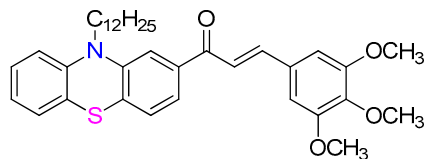


(E)-3-(4-chlorophenyl)-1-(10-dodecyl-10H-phenothiazin-2-yl)prop-2-en-1-one

HepG-2

7.14 ± 0.3*

45

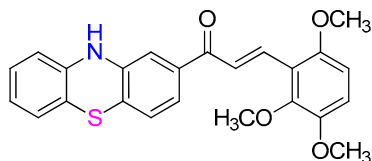


(*E*)-1-(10-dodecyl-10*H*-phenothiazin-2-yl)-3-(3,4,5-trimethoxyphenyl)prop-2-en-1-one

HepG-2

7.6 ± 0.2*

*Cisplatin 3.67±0.2
Doxorubicin 0.36±0.04



(*E*)-1-(10*H*-phenothiazin-2-yl)-3-(2,3,6-trimethoxyphenyl)prop-2-en-1-one

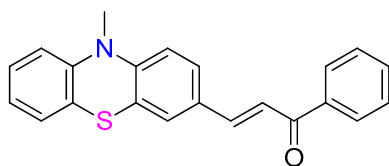
HSC-2

CC₅₀ = 8-64 μM

Caspase-3↑

apoptosis ↑ in
HSC-2

93



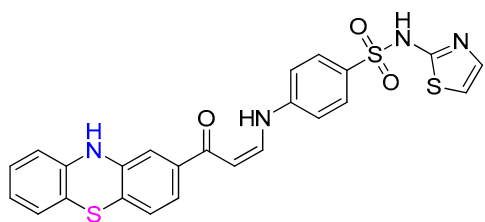
(*E*)-3-(10-methyl-10*H*-phenothiazin-3-yl)-1-phenylprop-2-en-1-one

MCF-7

LDH release↑

percentage of
viability of MCF-7↓

44



(Z)-4-((3-oxo-3-(10H-phenothiazin-2-yl)prop-1-en-1-yl)amino)-N-(thiazol-2-yl)benzenesulfonamide

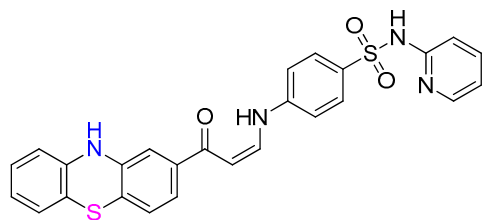
T47D

8.1*

Caspases-3,-8,-9↑

aromatase
inhibitory
activity↑,
apoptosis↑,
G1 cell cycle
arrest↑

94

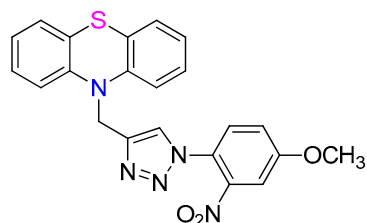


(Z)-4-((3-oxo-3-(10H-phenothiazin-2-yl)prop-1-en-1-yl)amino)-N-(pyridin-2-yl)benzenesulfonamide

8.8*

*Doxorubicin IC₅₀ 9.8

94



10-((1-(4-methoxy-2-nitrophenyl)-1H-1,2,3-triazol-4-yl)methyl)-10H-phenothiazine

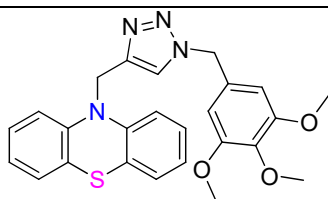
MGC-803

1.2

tubulin
polymerization↓

migration of MGC-
803 cell line↓

95

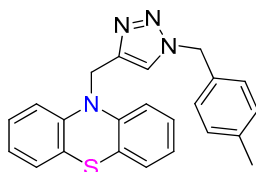


10-((1-(3,4,5-trimethoxybenzyl)-1H-1,2,3-triazol-4-yl)methyl)-10H-phenothiazine

MDA-MB-231,
MDA-MB-468,
MCF-7

1.7 ± 0.1*
1.2 ± 0.2*
0.8 ± 0.1*

MCF-7
apoptosis↑



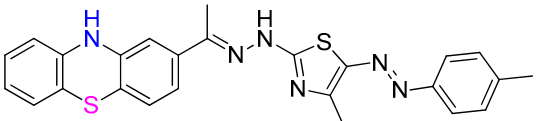
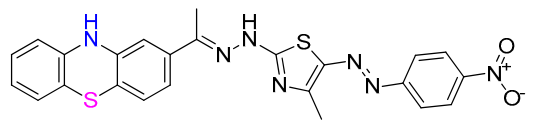
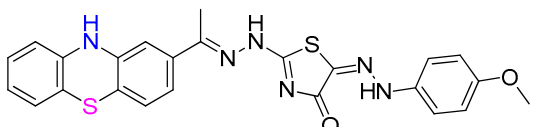
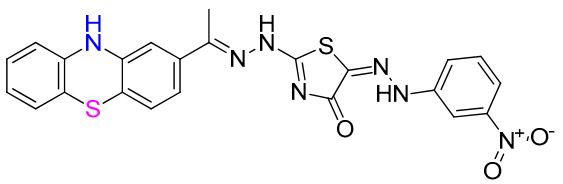
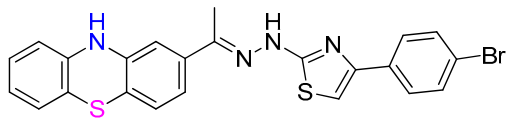
10-((1-(4-methylbenzyl)-1H-1,2,3-triazol-4-yl)methyl)-10H-phenothiazine

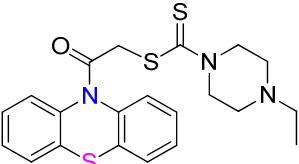
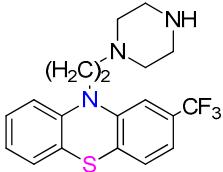
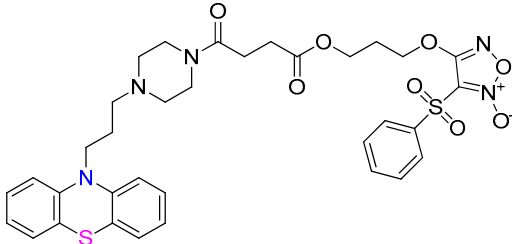
MDA-MB-231,
MDA-MB-468,
MCF-7

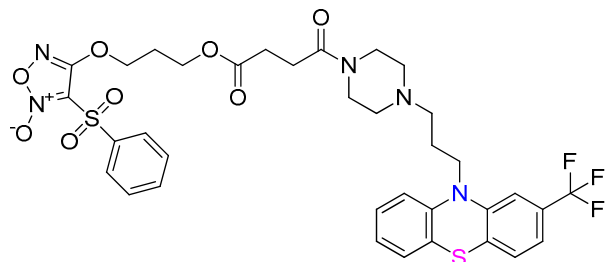
2.0 ± 0.2*
1.6 ± 0.3*
7.3 ± 1.1*

*5-Fu
MDA-MB-231, 10.8 ± 0.3
MDA-MB-468, 7.5 ± 0.2
MCF-7 = 12.7 ± 0.6

96

 2-((E)-1-(2-(4-methyl-5-((E)-<i>p</i>-tolyl diazenyl)thiazol-2-yl)hydrazono)ethyl)-10<i>H</i>-phenothiazine	HepG2, A549	10.30, 12.40*	97
 2-((E)-1-(2-(4-methyl-5-((E)-(4-nitrophenyl)diazenyl)thiazol-2-yl)hydrazono)ethyl)-10<i>H</i>-phenothiazine	HepG2, A549	18.1, 14.23*	97
 (<i>E</i>)-2-((<i>E</i>)-2-(1-(10<i>H</i>-phenothiazin-2-yl)ethylidene)hydrazinyl)-5-(2-(4-methoxyphenyl)hydrazono)thiazol-4(5<i>H</i>)-one	HepG2, A549	5.37, 6.91*	97
 (<i>E</i>)-2-((<i>E</i>)-2-(1-(10<i>H</i>-phenothiazin-2-yl)ethylidene)hydrazinyl)-5-(2-(3-nitrophenyl)hydrazono)thiazol-4(5<i>H</i>)-one	HepG2, A549	7.38, 9.78*	97
 (<i>E</i>)-2-(1-(2-(4-(4-bromophenyl)thiazol-2-yl)hydrazono)ethyl)-10<i>H</i>-phenothiazine	HepG2, A549	9.41, 13.9*	97
*Cisplatin IC ₅₀ A549 19.3 µg/mL HepG2 18.4 µg/mL			97

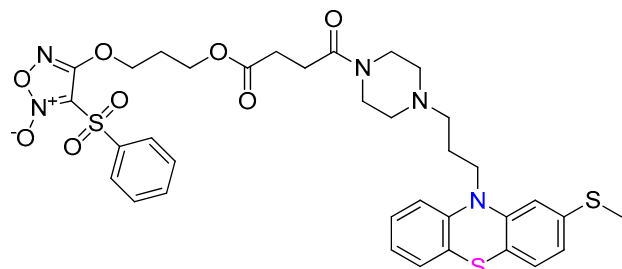
 2-oxo-2-(10H-phenothiazin-10-yl)ethyl 4-ethylpiperazine-1-carbodithioate	PC-3	antiproliferative activity 11.5 μ M/L		G ₁ -phase arrest $\uparrow$	65
 10-(2-(piperazin-1-yl)ethyl)-2-(trifluoromethyl)-10H-phenothiazine	Ca922, SCC2095	antiproliferative activity 4.9 $\pm$ 1.1 μ M/L	AMPK, ROS production, and caspases $\uparrow$, Ca922 xenograft $\downarrow$	autophagic cell death $\uparrow$, caspase-dependent apoptosis $\uparrow$	98
	Ca922, SCC2095	*trifluoperazine 14, 18 μ M			
 4-(3-((4-(4-(3-(10H-phenothiazin-10-yl)propyl)piperazin-1-yl)-4-oxobutanoyl)oxy)propoxy)-3-(phenylsulfonyl)-1,2,5-oxadiazole-2-oxide	SUM159 MDA-MB-231 MCF-7 SKBR-3 KG1	1.63 $\pm$ 0.31 11.25 $\pm$ 2.73 2.94 $\pm$ 0.99 13.57 $\pm$ 3.51 1.63 $\pm$ 0.31*	pNF- κ B-p65 $\downarrow$		99



4-(3-((4-oxo-4-(4-(3-(2-(trifluoromethyl)-10H-phenothiazin-10-yl)propyl)piperazin-1-yl)butanoyl)oxy)propoxy)-3-(phenyl sulfonyl)-1,2,5-oxadiazole-2-oxide

SUM159	2.93±0.20
MDA-MB-231	10.23±1.90
MCF-7	1.35±0.30
KG1	2.93±0.20*

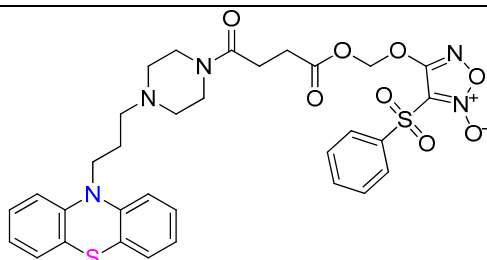
99



4-(3-((4-(4-(3-(2-(methylthio)-10H-phenothiazin-10-yl)propyl)piperazin-1-yl)-4-oxobutanoyl)oxy)propoxy)-3-(phenyl sulfonyl)-1,2,5-oxadiazole-2-oxide

SUM159	1.14±0.08
MDA-MB-231	3.62±0.93
MCF-7	0.84±0.10
SKBR-3	9.72±1.71
KG1	1.14±0.08*

99

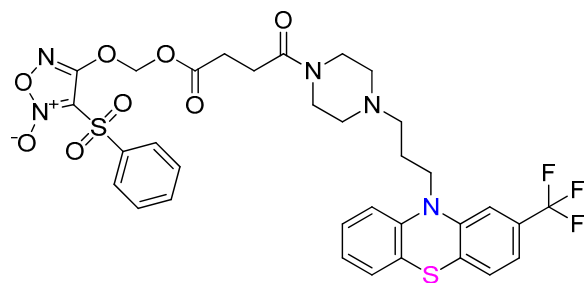


4-(((4-(4-(3-(10H-phenothiazin-10-yl)propyl)piperazin-1-yl)-4-oxobutanoyl)oxy)methoxy)-3-(phenylsulfonyl)-1,2,5-oxadiazole-2-oxide

SUM159	1.78±0.43
MDA-MB-231	1.60±0.54
MCF-7	3.23±0.26
SKBR-3	2.22±0.24
KG1	1.78±0.43*

pNF-κB-p65↓

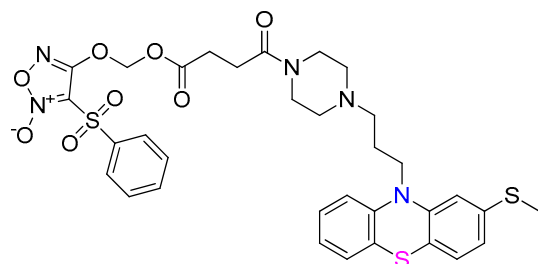
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4-(((4-Oxo-4-(4-(3-(2-(trifluoromethyl)-10*H*-phenothiazin-10-yl)propyl)piperazin-1-yl)butanoyl)oxy)methoxy)-3-(phenylsulfonyl)-1,2,5-oxadiazole-2-oxide

SUM159	2.20±0.58
MDA-MB-231	7.09±1.99
MCF-7	1.36±0.18
SKBR-3	1.51±0.06
KG1	2.20±0.58*

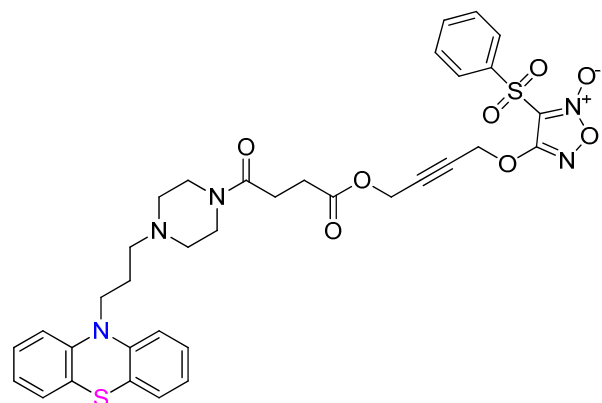
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4-(((4-(4-(3-(2-(Methylthio)-10*H*-phenothiazin-10-yl)propyl)piperazin-1-yl)-4-oxobutanoyl)oxy)methoxy)-3-(phenylsulfonyl)-1,2,5-oxadiazole-2-oxide

SUM159	1.20±0.24
MDA-MB-231	3.82±1.56
MCF-7	1.85±0.28
SKBR-3	3.86±0.13
KG1	1.20±0.24*

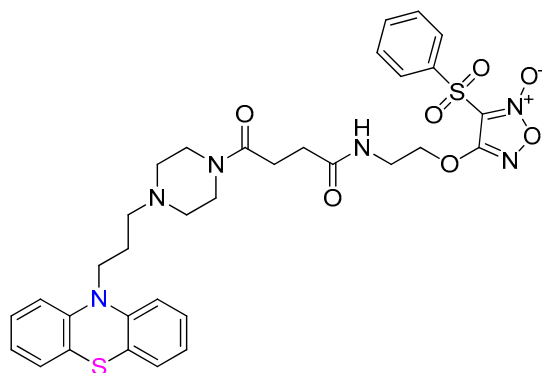
99



4-((4-((4-(3-(10*H*-phenothiazin-10-yl)propyl)piperazin-1-yl)-4-oxobutanoyl)oxy)but-2-yn-1-yl)oxy)-3-(phenylsulfonyl)-1,2,5-oxadiazole-2-oxide

SUM159	2.85±1.31
MDA-MB-231	6.40±2.86
MCF-7	1.55±0.16
SKBR-3	8.89±1.46*

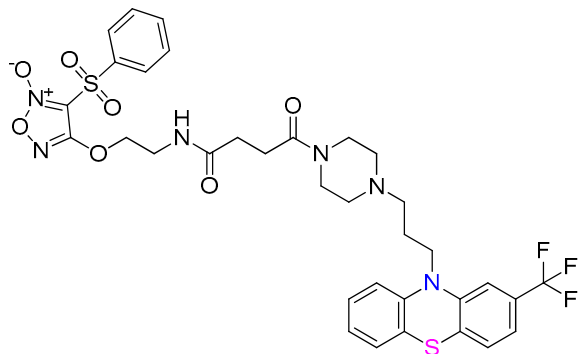
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4-(2-(4-(4-(3-(10*H*-phenothiazin-10-yl)propyl)piperazin-1-yl)-4-oxobutanamido)ethoxy)-3-(phenylsulfonyl)-1,2,5-oxadiazole 2-oxide

SUM159	4.17±1.38
MDA-MB-231	1.43±0.44
MCF-7	5.58±0.31
SKBR-3	4.01±0.90*

99



4-(2-(4-Oxo-4-(4-(3-(2-(trifluoromethyl)-10H-phenothiazin-10-yl)propyl)piperazin-1-yl)butanamido)ethoxy)-3-(phenylsulfonyl)-1,2,5-oxadiazole-2-oxide

SUM159
MDA-MB-231
MCF-7
SKBR-3

1.98±0.73

6.04±0.88

6.96±1.15

1.77±0.94*

*Trifluoperazine

SUM159 17.03±2.57

MDA-MB-231 21.58±2.45

MCF-7 11.33±0.80

SKBR-3 15.89±1.7

*Thioridazine

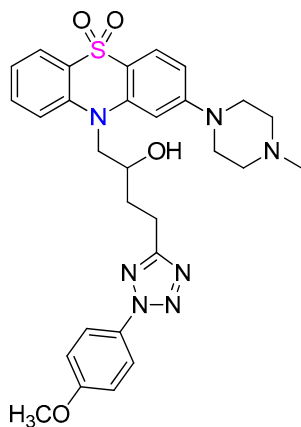
SUM159 14.51±2.90

MDA-MB-231

14.19±1.30

MCF-7 12.95±1.37

SKBR-3 18.23±3.00



10-(2-Hydroxy-4-(2-(4-methoxyphenyl)-2H-tetrazol-5-yl)butyl)-2-(4-methylpiperazin-1-yl)-10H-phenothiazine 5,5-dioxide

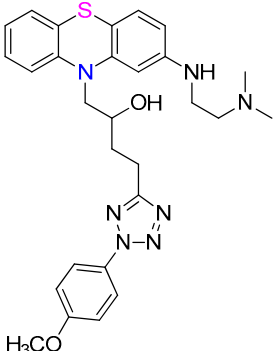
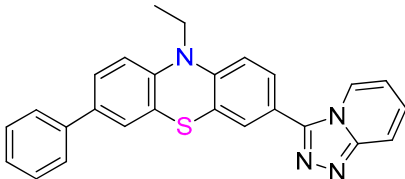
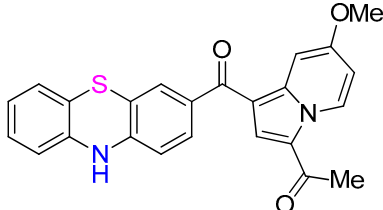
Colo 320

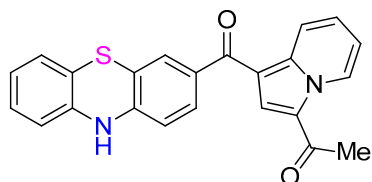
5.02

intracellular
rhodamine 123↑

apoptosis↑,
necrosis↑

100

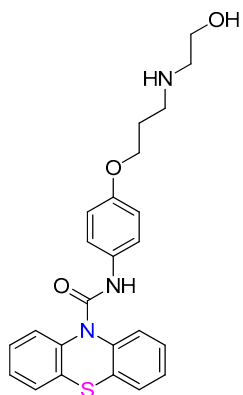
 1-(2-((2-(Dimethylamino)ethyl)amino)-10H-phenothiazin-10-yl)-4-(2-(4-methoxyphenyl)-2H-tetrazol-5-yl)butan-2-ol	Colo 320	2.52		100
 3-([1,2,4]triazolo[4,3-a]pyridin-3-yl)-10-ethyl-7-phenyl-10H-phenothiazine	MCF7, MDA-MB	6.2, 9.7	G ₂ /M accumulation↑, apoptosis↑	101
 1-(7-methoxy-1-(10H-phenothiazine-3-carbonyl)indolizin-3-yl)ethanone		IC ₅₀ (tubulin)=1.11 inhibition of tubulin polymerization at a 100 μM concentration 100%	tubulin polymerization ↓, FTase ↓ cell growth↓	102
		IC ₅₀ (FTase) = 0.39 Inhibition of Human FTase at a 100 μM concentration Phenstatin 3.43 (-)-Desoxypodo-phyllotoxin 1.76		



GI₅₀ (NCI-H522) = 1.8 nM;
 GI₅₀ (MDA-MB-435) = 1.8 nM)
 GI₅₀ (SNB-75) = 2.0 nM;
 GI₅₀ (A498) = 2.3 nM

102

1-(1-(10H-phenothiazine-3-carbonyl)indolizin-3-yl)ethanone



N-(4-(3-((2-Hydroxyethyl)-amino)propoxy)phenyl)-10H-phenothiazine-10-carboxamide

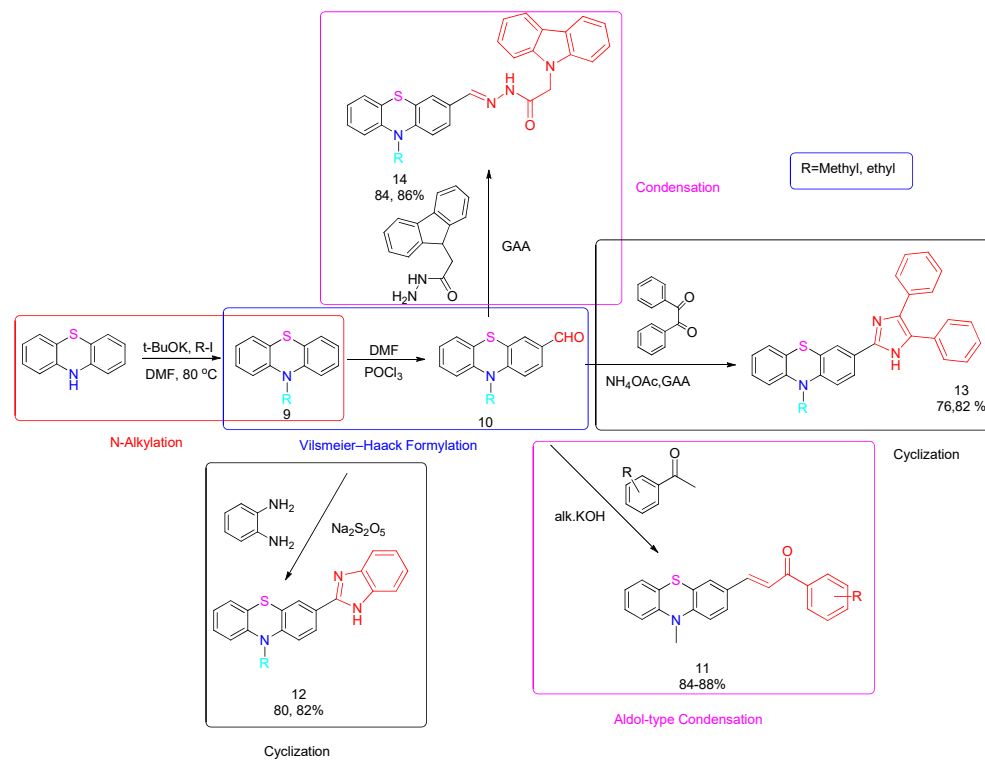
PC-3

12

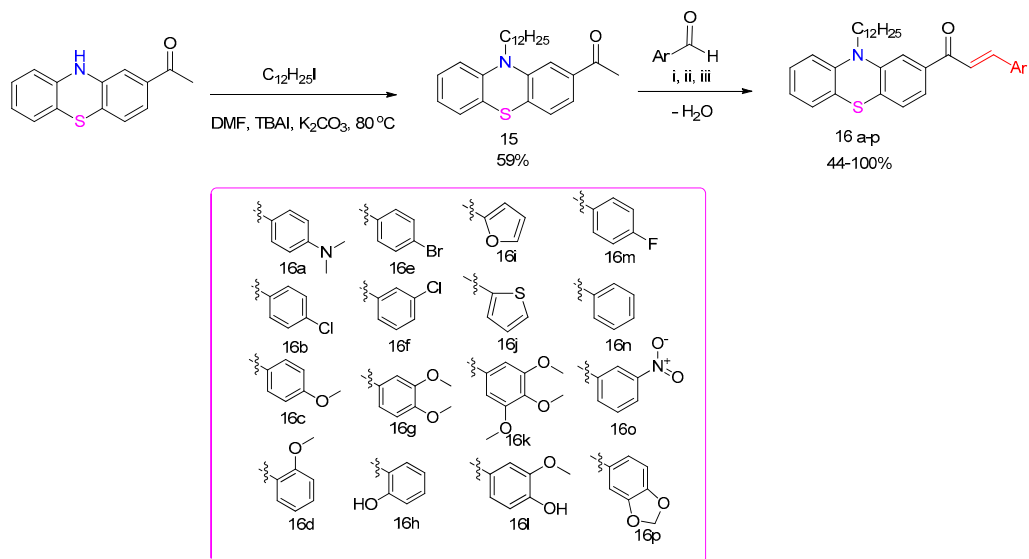
colony formation of
 MDA-MB-231↓,
 cell cycle was
 arrested at G₀/G₁
 phase↑,
 cell migration and
 invasion↓,
 caspase 3 and
 PARP↑

apoptosis↑

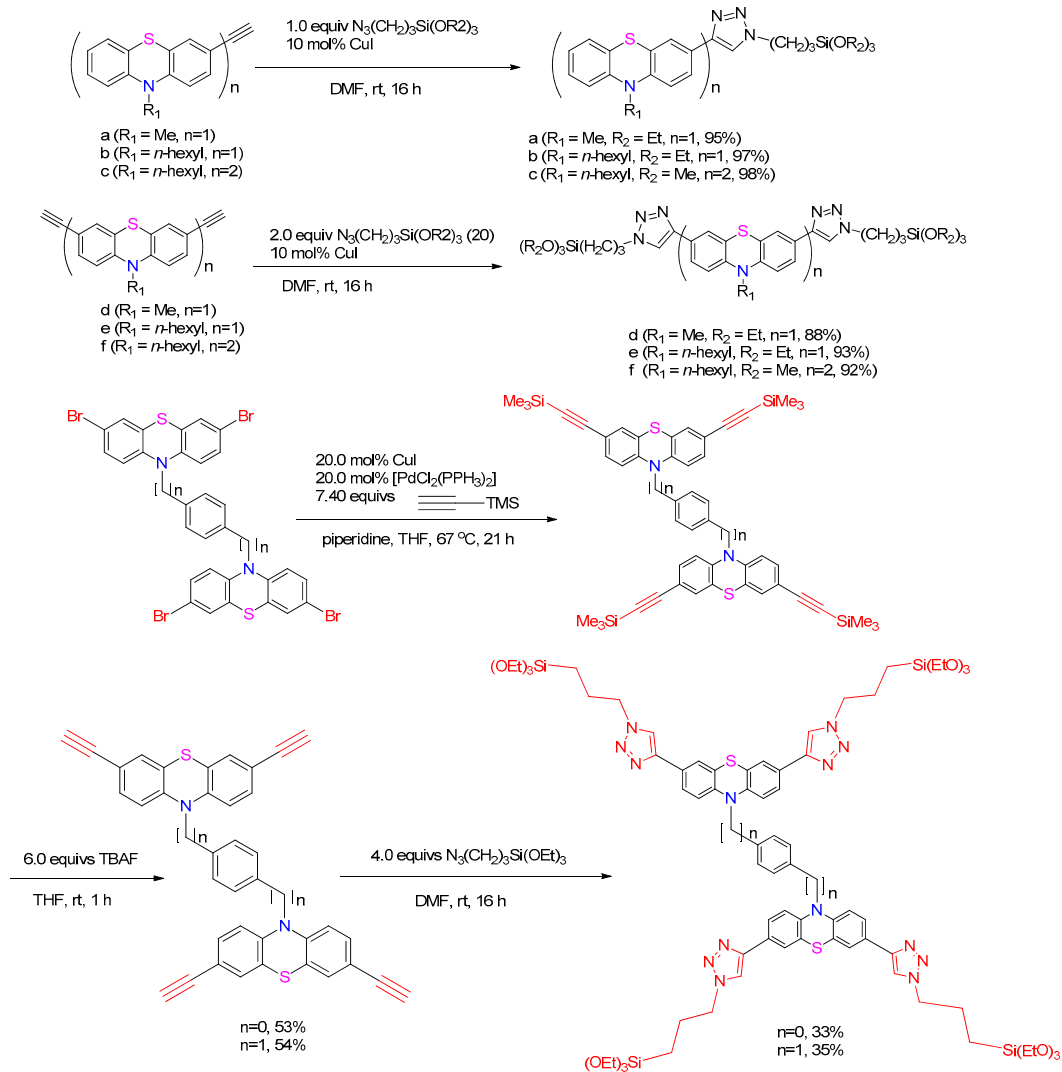
103



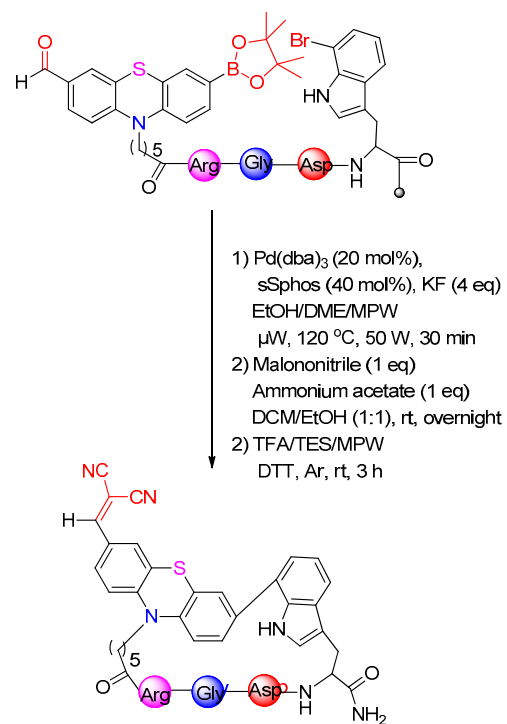
Scheme S1. Synthetic pathway for the preparation of phenothiazine compounds (**11-14**). Adapted from [55].



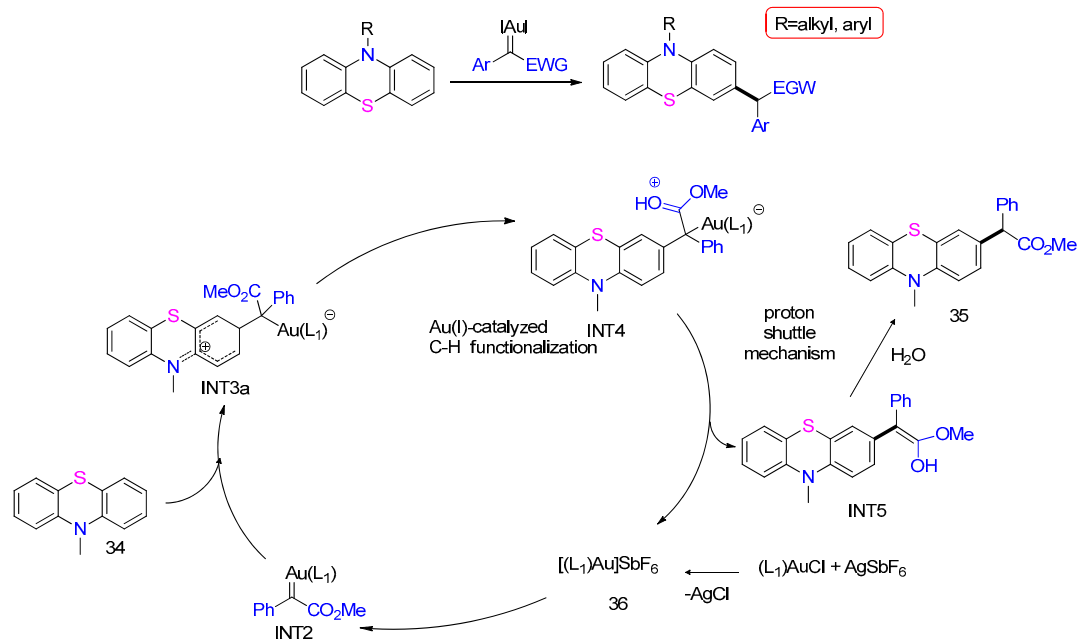
Scheme S2. Synthetic routes for chalcone derivatives **16a-p**; *i* = 5% alcoholic NaOH / rt / overnight; *ii* = ethanol-piperidine / reflux / overnight; *iii* = methanol / 50% aqueous KOH / rt / overnight. Adapted from [56].



Scheme S3. CuAAC synthesis of triazolyl conjugated triethoxysilylpropyltriazolyl (oligo)phenothiazines and tetrakis(triethoxysilylpropyltriazolyl)-substituted diphenothiazine dumbbells. Adapted from [78].



Scheme S4. Synthesis of cyclopeptide with an additional electron-withdrawing moiety by sequential on resin Suzuki/Knoevenagel reactions. Adapted from [83].



Scheme S5. Plausible catalytic cycle for the C-H functionalization reaction of phenothiazine. Adapted from [90].