Bioorg. Med. Chem. Lett. 41 (2021) 127997

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

Discovery of sertraline and its derivatives able to combat drug-resistant gastric cancer cell *via* inducing apoptosis

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ARTICLE INFO

Keywords:
Sertraline
Chemosensitizer
Drug-resistant
Gastric cancer
Apoptosis

ABSTRACT

Resistance phenomena during chemotherapy of tumor has been severely hampering the applications of chemotherapeutics. Due to advantage of drug repurposing, discovery of new chemosensitizers based on approved drugs is an effect strategy to find new candidates. Herein, we found antidepressant drug – sertraline, could sensitize drug-resistant gastric cancer cell (SGC-7901/DDP) with the IC_{50} value of 18.73 μM. To understand the structure–activity relationship and improve the activity, 30 derivatives were synthesized and evaluated. The IC_{50} value of the best compound was improved to 5.2 μM. Moreover, we found apoptosis induction and cell cycle arrest was the reason for the cell death of the drug-resistant cells after treatment of sertraline and derivatives, and PI3K/Akt/mTOR pathway was involved.

Introduction

Gastric cancer, a type of malignancies with high morbidity, has continuously caused large numbers of deaths each year.[1] Chemotherapy remains the principal therapy in the treatment of gastric cancer,[2] but the efficacy of traditional chemotherapeutic drugs remains suboptimal. First-line chemotherapeutic drugs for gastric cancer, including cisplatin, paclitaxel, etc,[2] inevitably end up with developing acquired drug resistance during treatment, which causes chemotherapy failure and cancer relapse.[3,4]

The mechanisms for the development of drug resistance are complicated.[5–7] Cancer cells can acquire resistance to a certain drug, such as tyrosine kinase inhibitors (TKIs) and frequently induce resistance while treating lung cancer patients.[8–10] This type of resistance is often evolved via acquired mutations in the target genes and/or changes in relative regulating pathways.[11] Meanwhile, some cancer cell lines show inherited or acquired resistance to multiple chemotherapeutic drugs, namely multiple drug resistance (MDR).[12] MDR is proved associated with the intrinsic or acquired high expression of "efflux pumps" such as P-glycoprotein or other "multidrug resistance-associated proteins" that exclude drug molecules out of cells, and lead to lowered intracellular drug concentration which is insufficient for treatment.[13,14]

Although distinct molecular mechanisms are found responsible for different types of drug resistance, the misregulation or inhibition of apoptosis process is recognized as the common epigenetic event highly relevant to the occurrence of drug resistance.[15,16] Therefore, the reactivation or reconstruction of apoptosis is pivotal to sensitize the resistant cells to chemotherapeutic drugs. Considerable amount of the adjuvant drugs developed for overcoming drug resistance, namely chemosensitizers, focus on the induction of apoptosis.[17–22]

On the other hand, most reported chemosensitizers are selected from existing drugs or their structural modified version, such as metformin,[17] aspirin,[18] verapamil,[19] etc. This novel strategy, known as drug repurposing, has attracted great attention in drug development, for its well-studied safety status as well as controllable research and development cost comparing with inventing new chemical entities.[23] In previous clinical studies, chemotherapy combined with antidepressant therapy using serotonin reuptake inhibitors (SSRI) can significantly improve the survival time and quality of life of cancer patients with depression.[24] Moreover, fluoxetine, a SSRI, has been repurposed as an MDR modulator for several resistant cell lines.[25–27] Another SSRI, sertraline, has also been proved to be efficient to sensitize multidrug resistant human ovarian tumor,[28] and the inhibition of extrusion pumps was suggested as the mechanism of its synergistic effects. Moreover, sertraline has also been proved its usefulness in sensitizing erlotinib-resistant non-small

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https://doi.org/10.1016/j.bmcl.2021.127997
Received 5 January 2021; Received in revised form 9 March 2021; Accepted 22 March 2021
Available online 26 March 2021

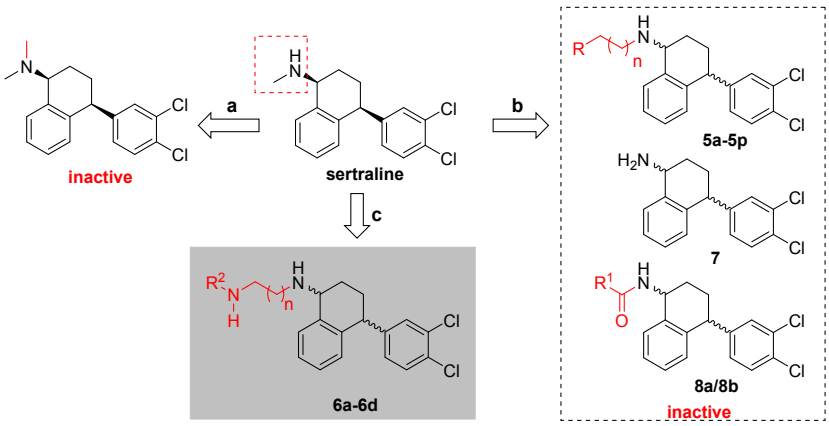


Fig. 1. The design concept of sertraline derivatives.

cell lung cancer, via inducing autophagy and apoptosis.[29] These results have demonstrated the potential of SSRIs to be repurposed as versatile chemosensitizers. However, it's noticeable that the experimental concentrations of the chemicals are high, thus respective doses in clinical treatment would probably raise some safety issues.

In this work, we proved that sertraline exhibited moderate sensitizing effects on drug resistant gastric cancer cells, via inducing apoptosis. As a classic antidepressant drug, sertraline has been widely prescribed and causes only slight and tolerable adverse effects in most patients,[30] thus is promising to be repurposed as a supportive therapy in gastric cancer treatment, to defeat or prevent the drug resistance raised in chemotherapies. Moreover, to further improve its efficacy and safety, structural modification of sertraline to upgrade the activity and lower the therapeutic dose is necessary. Our work has established a concise *de novo* synthetic route to access several sertraline-derived compounds. The sensitizing effects of the obtained compounds were evaluated over SGC-7901/DDP, a gastric cancer cell line resistant to cisplatin (DDP), and several compounds with obviously improved activity were obtained through the screening. We further evaluated the apoptosis inducing effects of the compounds and explored the underlying mechanism, in which we found the classic PI3K/Akt/mTOR pathway[31,32] was responsible in regulating the effects inspired by sertraline and its derivatives.

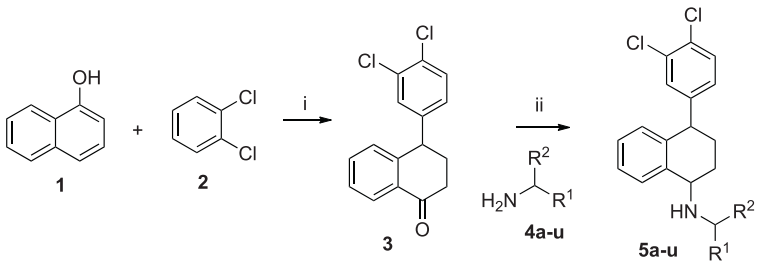
The preliminary studies to modify sertraline by methylation of its secondary amine moiety (Fig. 1, a) ended up with completely loss of antiproliferative effects (data not shown), indicating the necessity of the active *N*—H to antitumor activity, which might generate a vital hydrogen bond. Therefore, modification of sertraline was focused on altering the other substituent on the nitrogen, retaining the active hydrogen. Attempts of direct demethylation from sertraline to obtain the primary amine for modification turned out difficult, therefore we established a *de novo* synthetic route from commercially available α-naphthol **1** and 1,2-dichlorobenzene **2** (Scheme 1). Intermediate naphthalenone derivative **3** could be smoothly obtained in a high yield (80%). Then the different substituted amines **4** were reacted with **3** to afford derivatives **5** via a reductive amination process. Except for a series of secondary amines (**5**), other amine/amide types retaining N—H were also synthesized, including primary amine **7** and its acylation products **8**. All these structures were characterized with ^{1}H NMR, ^{13}C NMR and HRMS. Relative configuration of **8a/8a'** was assigned according to literature[33] and conformed by ^{1}H–^{1}H NOESY analysis. Other products were assigned by analogy.

Subsequently, the antiproliferative effects of the derivatives were tested over cisplatin-resistant gastric cancer cell line SGC-7901/DDP together with cisplatin, to evaluate their sensitizing activities. Initial evaluation was performed in a single concentration, 20 μM, with 15 μM DDP.[34,35] Since two diastereomers were obtained in the reductive amination step, *trans* and *cis*-products **5b/5b'**, **6a/6a'**–**6c/6c'** and **7/7′** were comparatively evaluated. The inhibition rate indicated that the activity of diastereomers were almost identical, thus screening of the obtained derivatives was mainly performed using the *trans*-products as representative (Fig. 2). Firstly, several alkyl groups were introduced as the *N*-substituents, only the butyl substituted **5b** turned out to exert obvious sensitizing effect, other alkyl groups were futile on synergizing with DDP, especially the branched alkyls. Next, benzyl and substituted benzyl groups were introduced to obtain **5h–5p**. Except for benzyl/4-OMe-benzyl substituted derivatives **5h**/**5k** which demonstrated slight sensitizing effects, other electron-donating or -withdrawing benzyls all failed to improve the activities of the derivatives, and some products even seemed to further withdraw the antiproliferative effect of DDP. Disappointingly, all products of the abovementioned structural modification exerted inferior effects compared with sertraline (Ser) at 20 μM (Fig. 2). Moreover, changing the amine type of sertraline to primary amine or amide groups (**7** and **8**) also resulted in reduced activities (Fig. 1, b).

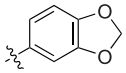
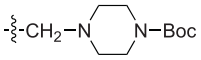
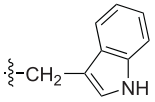
Considering the positive effects of the presumed hydrogen bonds, substituents containing extra active hydrogens were introduced, including **5u** and **6a**–**6d**, via deprotection of *N*-Boc after the reductive amination step. Fortunately, derivatives with primary amine groups (**6a**–**6c**) or *N*-unprotected piperazine (**6d**) exerted excellent activities as designed, which might generate the expected extra hydrogen bonds (Fig. 1, c).

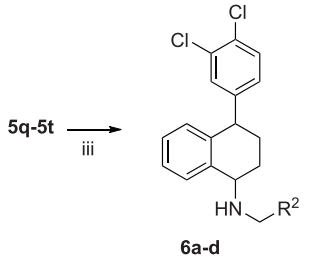
Next, products which were more effective than sertraline at 20 μM, including **6a**–**6c** (both isomers), **5t** and its deprotected product **6d**, were further evaluated in a dose-dependent manner (C = 1.0, 2.0, 4.0, 8.0, 12, 16, 20, 24 μM), with IC_{50} values calculated (Table 1). Comparing with sertraline (IC_{50} = 18.73 ± 0.46 μM), these derivatives were significantly improved in their sensitizing activity, which showed generally lower IC_{50}. Among them, H-bonds modified *trans*-**6b** and *trans*-**6d** demonstrated the best activities, with IC_{50} values of 6.28 ± 0.50 μM and 5.20 ± 0.36 μM, therefore they were selected as representatives for further investigation. We also evaluated their cytotoxicity towards GES-01, an immortalized gastric epithelial cell line, and found **6d** showed moderate selectivity between cancer cell line and normal cell line. Moreover, the predicted pharmacokinetic parameters also suggested **6d** might be a good lead.

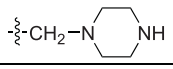
Reactivating the apoptosis process to induce drug-resistant cell death is the main mechanism of action for most chemosensitizers. To preliminarily explore the mechanism of sertraline-induced sensitizing effect, we first tested whether sertraline and the derivatives could induce apoptosis in SGC-7901/DDP cells. DDP (15 μM) exhibited identical apoptotic rate with the control group, while co-administration with sertraline (C = 8 μM) exhibited moderate apoptosis inducing activity, with 20.9% apoptotic rate. The derivatives **6b** and **6d** exhibited improved activity at 3 μM concentration (Fig. 3A and 3B). Meanwhile, the caspase protein family, which is closely relevant to programmed cell death, was also analyzed to indicate the apoptosis level. The 'initiator

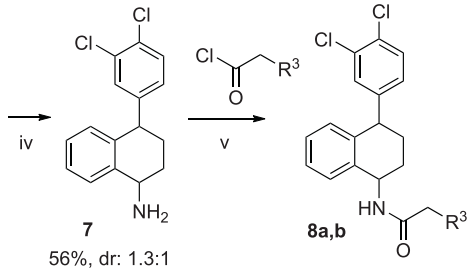


Scheme 1. Synthesis of sertraline analogues. Reagents and conditions: (i) $AlCl_3$, 100 °C, 2.5 h; (ii) Ti$(OiPr)_4$, $NaBH_3CN$, Me_2CHOH, 85 °C, 8 h; (iii) TFA, DCM, rt, 3.5 h; (iv) NH_4OAc, $NaBH_4$, Me_2CHOH, 85 °C, 16 h; (v) $NaHCO_3$, DCM, 0 °C, 6 h. *a*. Isolated yield for both isomers. *b*. Diastereomeric ratio (dr, trans:cis) was detected by ^1H NMR analysis of crude products. Relative configuration of **8a**/**8a**' were determined by ^1H–^1H NOESY analysis, and other products were assigned by analogy. *c*. Products yielded from *trans* and *cis*-products, respectively. *d*. Product of *trans*-**7**.

entry	compound	R^1	R^2	yield (%) [a]	dr [b]
1	**5a**	-H	$-CH_2CH_3$	47	1.8:1
2	**5b**	-H	$-(CH_2)_2CH_3$	81	1:1
3	**5c**	-H	$-(CH_2)_4CH_3$	56	1.2:1
4	**5d**	-H	$-CH(CH_3)_2$	48	1.7:1
5	**5e**	-H	-cyclohexane	17	1.9:1
6	**5f**	-H	$-(CH_2)_3C_6H_5$	14	1.5:1
7	**5g**	-cyclopropane	-cyclopropane	62	1.7:1
8	**5h**	-H	$-C_6H_5$	44	1.6:1
9	**5i**	-H	-1-naphthalene	81	1:1
10	**5j**	-H	$-4\text{-}CH_3\text{-}C_6H_5$	34	0.7:1
11	**5k**	-H	$-4\text{-}OCH_3\text{-}C_6H_5$	27	1.2:1
12	**5l**	-H	$-3\text{-}OCH_3\text{-}C_6H_5$	32	3.8:1
13	**5m**	-H		13	2.8:1
14	**5n**	-H	$-3,4\text{-diOMe-}C_6H_5$	59	2:1
15	**5o**	-H	$-3\text{-}CF_3\text{-}C_6H_5$	10	0.5:1
16	**5p**	-H	$-3,4\text{-diCl-}C_6H_5$	21	1:1
17	**5q**	-H	$-CH_2NHBoc$	81	1:1
18	**5r**	-H	$-(CH_2)_3NHBoc$	57	1.7:1
19	**5s**	-H	$-(CH_2)_5NHBoc$	49	1.5:1
20	**5t**	-H		43	1.4:1
21	**5u**	-H		10	2:1



	R^2	yield (%) [a]
6a/6a' [c]	$-CH_2NH_2$	83/80
6b/6b' [c]	$-(CH_2)_3NH_2$	58/65
6c/6c' [c]	$-(CH_2)_5NH_2$	82/89
6d [c]		85



56%, dr: 1.3:1

	R^3	yield (%) [a]
8a [d]	-H	19
8b [d]	$-(CH_2)_2Cl$	17

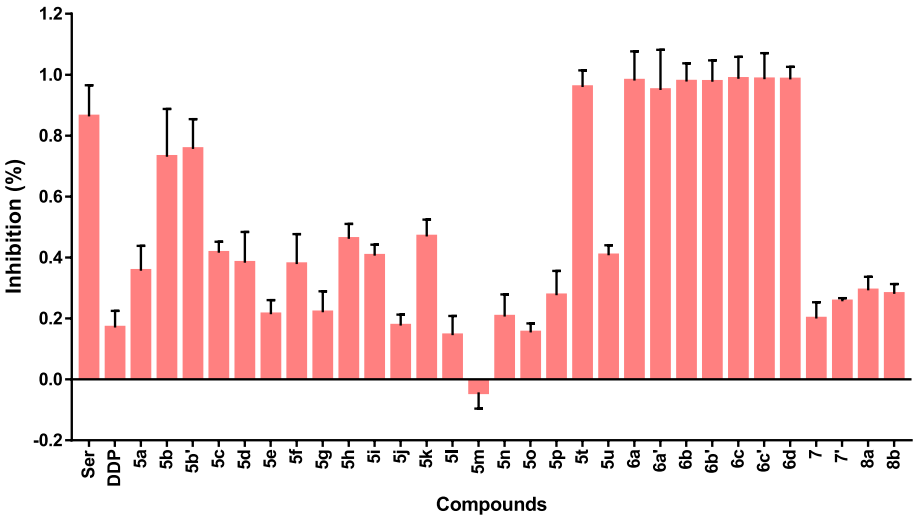
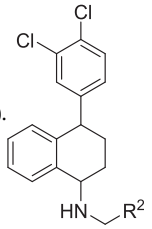


Fig. 2. Inhibition rate of sertraline and indicated derivatives (20 μM) to the proliferation of SGC-7901/DDP cells with DDP (15 μM). (n = 3).

Table 1
Evaluation of the antiproliferative effects of the indicated sertraline derivatives and respective IC_{50} (n = 3).



Entry	Compound	cis/trans	R^2	IC_{50}[a]
1	Sertraline (Ser)	cis	H	18.73 ± 0.46
2	**5t**	trans	—CH_2–N⟨⟩N–Boc	17.05 ± 0.82
3	**6a**	trans	CH_2NH_2	10.96 ± 0.51
4	**6a'**	cis	CH_2NH_2	10.69 ± 0.41
5	**6b**	trans	$(CH_2)_3NH_2$	6.28 ± 0.50
6	**6b'**	cis	$(CH_2)_3NH_2$	6.30 ± 2.46
7	**6c**	trans	$(CH_2)_5NH_2$	11.10 ± 0.65
8	**6c'**	cis	$(CH_2)_5NH_2$	18.90 ± 0.51
9	**6d**	trans	—CH_2–N⟨⟩NH	5.20 ± 0.36

[a] IC_{50} was tested based on the proliferation of SGC-7901/DDP cells with DDP (15 μM).

caspase' – caspase 9 and cleaved-caspase 9 (Cl-caspase 9), as well as the 'effector caspase' – caspase 3 and Cl-caspase 3, were chosen as representatives to be examined using Western blotting assay. The results showed dose-dependent upregulated level of Cl-caspase 3 after administrating sertraline (8, 16 μM) and derivatives (3, 6 μM), while the total caspases 3 were not obviously changed (Fig. 3C and 3D). These results suggested that sertraline and derivatives could sensitize the drug-resistant cells and induce cell death via reactivating apoptosis.

Meanwhile we examined the cell cycle distribution. DDP (15 μM) induced no cell cycle change comparing with the control group, while sertraline (8, 16 μM) and derivatives (3, 6 μM) caused obvious cell cycle arrest at G0/G1 phase at high percentages, which was accordant with the apoptosis results (Fig. 4).

The remarkable activities of sertraline derivatives on apoptosis upregulation and cell cycle arrest encouraged us to explore the underlying mechanism. It is well recognized that PI3K/Akt/mTOR pathway plays a vital role in regulating programed cell death, so we first tested if this pathway was involved in the effects of sertraline. Protein expression of the key kinases in this pathway, including PI3K, Akt, mTOR and their phosphorylated forms were examined after administrating DDP (15 μM) with or without sertraline (8, 16 μM) and derivatives (3, 6 μM) in the SGC-7901/DDP cells (Fig. 5). The activated forms of these marker proteins were generally downregulated after administration, especially at high doses. Importantly, phosphorylated forms of PI3K showed significant changes, while the total protein expressions were almost the same level. It could be speculated that PI3K/Akt/mTOR pathway, especially the inhibition of PI3K activated form might participate in regulating sertraline-induced apoptosis and cell cycle arrest, which would provide evidence for further mechanism study to figure out the pharmacological target of sertraline and derivatives.

In summary, we have discovered that an antidepressant drug – sertraline, could be repurposed to sensitize drug-resistant gastric cancer cell (SGC-7901/DDP). Besides, as an 'old' drug, sertraline is reliable in safety, so we suppose that it could be appropriate to be used as a 'new' adjuvant therapy, for re-sensitizing drug resistant gastric cancer. Nevertheless, insufficient activity of sertraline hampers its potential utilization. Therefore, in this manuscript we modified the molecule to obtain more active derivatives, and evaluated their sensitizing activity in SGC-7901/DDP cells. We preliminarily figured the structure–activity relationship after synthesizing and screening 30 derivatives, and selected 2 best molecules with the lowest IC50 values for further mechanism study. We confirmed that sertraline and its derivatives induced apoptosis and cell cycle arrest, leading to programed cell death of the SGC-7901/DDP cells. Moreover, it was found that the PI3K/Akt/mTOR pathway was involved in the effects of sertraline and derivatives, regulating the programed cell death. In summary, our findings provided active compounds and theoretical bases for sertraline to be repurposed as potentially novel chemosensitizers in drug-resistant gastric cancer treatment.

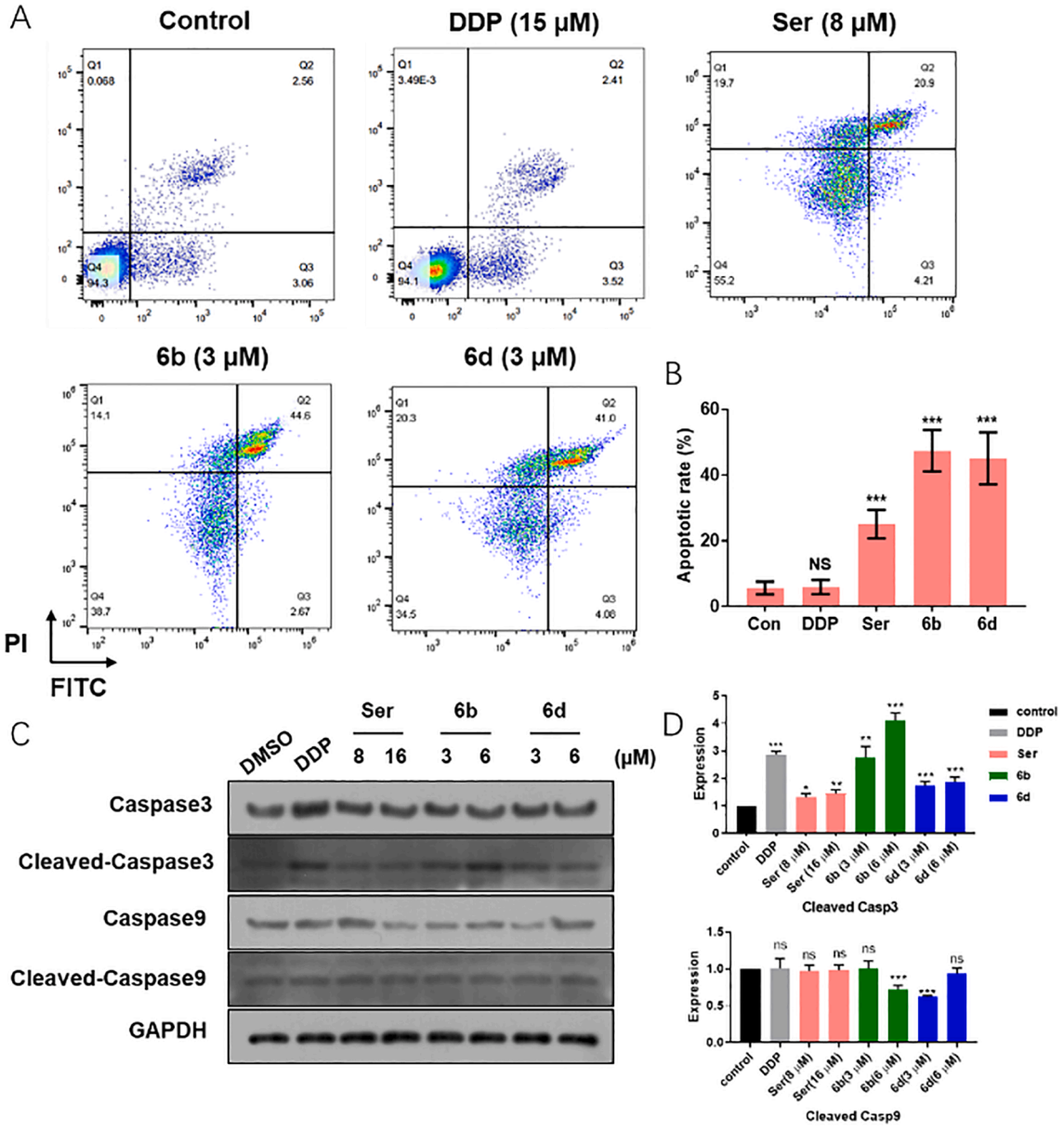


Fig. 3. Apoptosis inducing effects of sertraline and indicated derivatives. A. Flow cytometry figures of apoptosis. B. Apoptotic rates. C. Protein expression of caspase 3/9 and cleaved-caspase 3/9 after administrating sertraline and derivatives. D. Quantification of protein expression (n = 3, $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$, NS no significance).

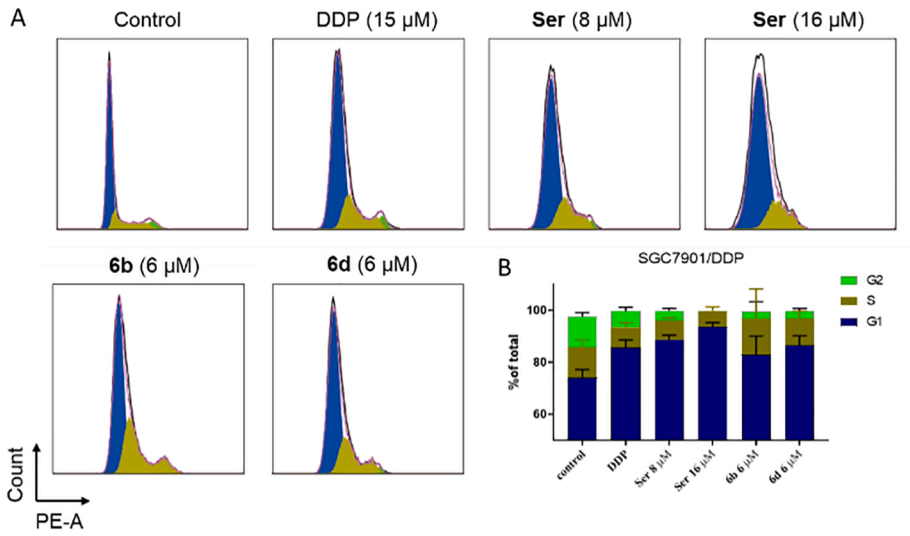


Fig. 4. Cell cycle arresting effects of sertraline and indicated derivatives. A. Flow cytometry figures of cell cycles. B. Quantification of cell cycle distribution.

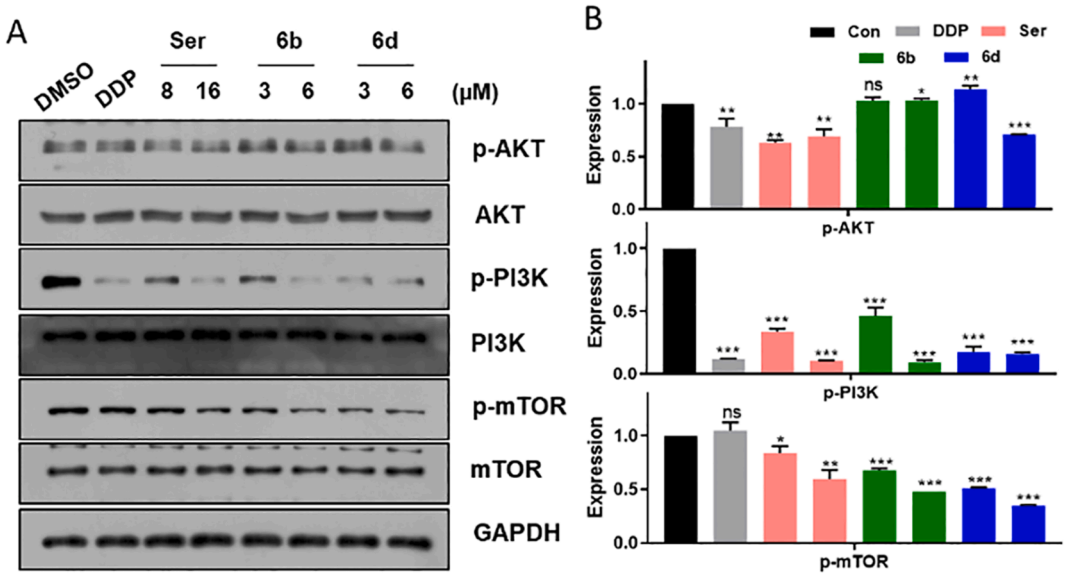


Fig. 5. Influence of sertraline and derivatives on protein expression of key kinases in PI3K/Akt/mTOR pathway. A. Protein expression after administrating sertraline and indicated derivatives. B. Quantification of protein expression (n = 3, $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$, NS no significance).

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

We are grateful for the financial support from the National Key R&D program of China (2018YFA0507900), National Natural Science Foundation of China (22007100), Chongqing Young Top Talents Training Plan, and Young Talents Training Program of Third Military Medical University (2020XQN07).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bmcl.2021.127997.

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