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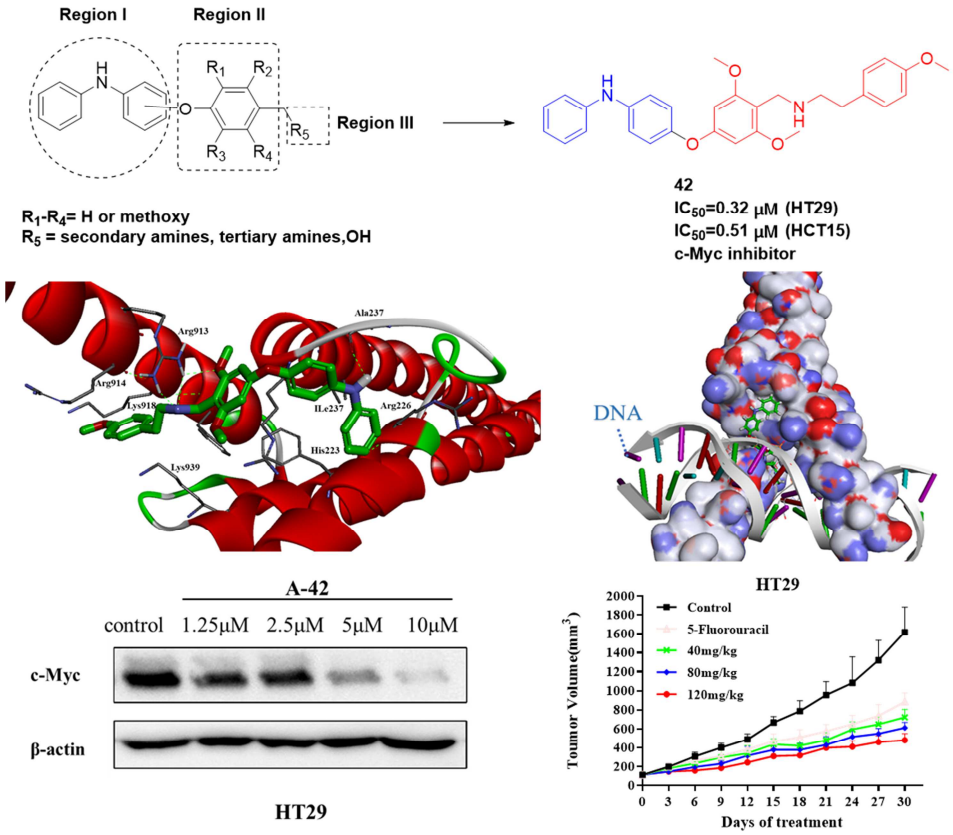
Graphical Abstract:



The 4-(3,5-dimethoxy-4-(((4-methoxyphenethyl)amino)methyl)phenoxy)-N-phenylaniline (**42**) as a novel potent c-Myc inhibitor was identified. The results demonstrated that **42** showed good binding affinity to c-Myc/MAX dimerization and DNA binding, downregulation of c-Myc expression level, and exhibited excellent antitumor activity in *vitro* and *vivo* with low toxicity.

Discovery of 4-(3,5-dimethoxy-4-(((4-methoxyphenethyl)amino)methyl)phenoxy)-N-phenylaniline as a novel c-Myc inhibitor against colorectal cancer in *vitro* and in *vivo*

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Abstract： Proto-oncogene c-Myc plays an essential role in the development of colorectal cancer (CRC), since downregulation of c-Myc inhibits intestinal polyposis, which is the most cardinal pathological change in the development of CRC. Herein, a series of novel phenoxy-N-phenylaniline derivatives were designed and synthesized. The cytotoxicity activities of all the derivatives were measured by MTT assay in different colon cancer cells, 4-(3,5-dimethoxy-4-(((4-methoxyphenethyl)amino)methyl)phenoxy)-N-phenylaniline (**42**) was discovered, the lead compound **42** with excellent cytotoxicity activity of IC_{50} = 0.32 μM, IC_{50} = 0.51 μM , in HT29 and HCT 15 cells, respectively. Compound **42** had a good inhibitory activity of c-Myc/MAX dimerization and DNA binding. Besides, compound **42** could effectively induce apoptosis and induced G2/M arrest in low concentration and G0/G1 arrest in high concentration to prevent the proliferation and differentiation in colon cancer cells. Western blot analysis confirmed the **42** strongly down-regulated expression of c-Myc. Furthermore, during 30 days treatment **42** exhibited excellent efficacy in HT29 tumor xenograft model without causing significant weight loss and toxicity. Consequently, **42** could be a promising drug candidate for CRC therapy.

Key words: colorectal cancer, c-Myc inhibitor, anti-CRC

1. INRODUCTION

Globally, colorectal cancer (CRC) is the second leading cause of cancer death, and the second most common cancer in women and the third most common in men. According to Globocan[1], the global prevalence of colorectal cancer in 2018 was estimated at over 6.3 million, with 1.8 million newly diagnosed and caused 880 792 deaths. The World Economic Forum estimated the total costs associated with colorectal cancer in 2010 to be approximately USD 31.6 billion, CRC resulted in a significant economic burden on patients and society[2-4]. Even though an increasing number of potentially curative treatments including chemotherapy agents, surgery, radiotherapy and molecular targeting therapies have been developed for CRC, the clinical prognosis still remain unsatisfactory, especially as CRC patients with metastases[5-8]. Furthermore, tumor heterogeneity leads to a significant consequence of resistant responses to chemotherapies and targeted therapies. The current first-line drugs for colorectal cancer patients, such as irinotecan, 5-Fluorouracil and its derived prodrugs, platinum drugs, etc[7, 8]. However, all of them have poor clinical efficacy, poor patient prognosis and serious drug resistance. Therefore, seeking for a new and effective drug is an enormous challenge for the therapy of CRC in the future.

C-Myc is the member of the Myc proto-oncogene family, a frequent genetic abnormality seen in CRC is the elevated expression of c-Myc, and the importance of c-Myc expression in CRC has been demonstrated in both studies of transgenic mice and clinical research, including tumor growth, replication, metabolism, differentiation, and apoptosis[9-14]. Downregulation of c-Myc can inhibit intestinal polyposis, which is the most important lesion in the process of colon cancer[10, 15, 16]. Thus, c-Myc inhibitors could help to suppress the initiation and progression of tumors. Recently, lots of c-Myc inhibitors were discovered including Myc-Max protein-protein interactions[17-19], such as 10058-F4, 10074-G5, SF-4-017, NUCC-0176242, or Myc-Max protein-DNA binding interactions[20, 21], such as Mycro 3, KJ Pyr 9, or binding to c-Myc G-quadruplex(G4) stabilizers[22, 23], such as Indenoisoquinoline 5, IZCZ-3, etc. Despite plenty of c-Myc inhibitors (shown in **Figure 1**) reported, there is no anti-Myc drug clinically available. Moreover, many of the known c-Myc inhibitors are not suitable for clinical studies because of low potency or poor antitumor activity in *vivo*[24, 25]. Thus, discovery of more novel c-Myc inhibitors, particularly with novel scaffolds is still necessary at present.

The c-Myc protein is the member of intrinsically disordered (ID) proteins[26, 27], which is characterized by a lack of stable structure and extensive backbone flexibility[28-30]. It is a relevant yet challenging target for drug discovery[31-33]. In an effort to seek novel c-Myc inhibitors, c-Myc–Max interactions inhibitors are most valuable for clinical research[34-37]. We initially studied the core structures of these small molecular inhibitors, and found most of these inhibitors contained a long molecular structure, because of the c-Myc-Max dimer interface was a left-handed, parallel and four-helix bundle, with each monomer consisted of two R-helices separated by an annulus[28, 38].

To identify novel inhibitors, biphenyl group[39-41] and diphenylamine group[42-46] were found in a great many of antitumor drugs with good biological activities, we designed by incorporation of the core structure a long molecular composed of three benzene rings. Therefore, we synthesized a series of fused 3(or4)-(phenoxy)-N-phenylaniline derivatives. In this study, we discovered a novel c-Myc inhibitor compound **42** that potently decreased the expression of c-Myc

protein verified by western blot. In *vitro* antiproliferative activity showed that compound **42** showed significant cytotoxicity in several colon cancer cells, especially in HT29 cells (IC_{50}= 0.32 μM) and HCT15 cells (IC_{50}= 0.51 μM). The lead compound **42** can induce apoptosis for HT29 and HCT15 cell lines and significantly induce G0/G1 arrest in high concentration and G2/M in low concentration. In *vivo* HT29 xenograft model study showed that compound **42** could significantly inhibit tumor growth without obvious toxicity.

On the basis of these findings, in *vivo* administration of compound **42** as c-Myc inhibitor for the treatment of colorectal cancer resulted in good anti-tumor activity and low toxicity. Thus, compound **42** represents a new class of c-Myc inhibitors as potential clinical agents against CRC.

2. RESULTS AND DISCUSSION

2.1. Design and synthesis of N-phenylaniline derivatives

With considering the good anti-tumor activities of these c-Myc/MAX inhibitors, we studied the core group of these inhibitors. Regarding the specificity of c-Myc/MAX protein binding[28, 34, 37], we designed and synthesized N-phenylaniline derivatives with skeletal transition based on the original small molecule c-Myc/MAX inhibitors. A great number of studies on the structural modifications based on the N-phenylaniline, and the incorporation with the N-phenylaniline may enhance biological activities significantly[47-51]. However, there were few studies on small molecular inhibitors of c-Myc. In order to design N-phenylaniline derivatives with a better biological activity and novelty, we designed and synthesized 3(or4)-(phenoxy)-N-phenylaniline derivatives shown in **Scheme1**.

The chemistry efforts to obtain **42** and a series of analogues are outlined in **Schemes 2-3**[52-55]. First, we synthesized 4-fluoro-2,6-dimethoxybenzaldehyde(**3**) by Vilsmeier-Haack reaction[52] with commercial compound **2**. Then, 3-(phenylamino)phenol(**5**) was prepared by 3-aminophenol and bromobenzene via Buchwald–Hartwig coupling reaction[53]. Subsequently, in the construction of the key intermediates **6a-6d**, we screened out a mild reaction condition, compound **5**, K_2CO_3 and 4-Fluorobenzaldehyde with different substituents under argon atmosphere in anhydrous DMSO was stirred at 100 ^oC for 3 h, the yields of desired compound were 70%-80%. Finally, these intermediates were stirred with different amines in the presence of sodium triacetoxyborohydride, under argon atmosphere in anhydrous DMF at 80^oC, to afford final compounds **7-38** with 45%-60% yields, as indicated in **Scheme 1**. Analogously, compounds **42-45** were synthesized following the synthetic route depicted in **Scheme 2**.

2.2. In *vitro* cell viability

In order to assess the cytotoxicity of these final products, the cytotoxicity on HCT116, HCT15, HT29, DLD-1, SW620 were tested by MTT[56-58] and the results achieved are shown in **Table 1**. Cisplatin and 5-Fluorouracil were effective drugs used in the clinical treatment of CRC[7, 8], so we chose them as positive drugs in the MTT test.

Firstly, we studied compounds **7-16** with R5 group bearing different aliphatic alkylamine substituents. R5 appendage carrying hydrophobic groups showed anti-proliferation activity against HT29, HCT15, DLD-1 cancer cell lines. Furthermore, we found that compound **22** showed an outstanding antiproliferative activity in five CRC lines. To further investigate the activity relationship (SAR) of R5 with extended chain length, the R5 groups were replaced by various

substituents of 4-phenylethylamine groups. Among these molecules (**27-32**), the compound **32** exhibited excellent activities in HT29, HCT15, HCT116, DLD-1 cell lines with IC_{50} values of 1.02 μM, 1.25 μM, 0.98 μM, 1.12 μM, respectively. Next, we discussed the effects of the R5-phenyl with methoxyl at C2-position and C3-position. As a result, the activities of the compounds were not increased significantly. Even though, we altered the linker length of R5 group and the pattern substitution of methoxyl groups in **Region** □, but no more active compounds were found.

Intriguingly, we changed the relative position of the aniline moiety relative to the oxygen that went from relative position 1,3 to 1,4 within **Region** □, and discussed the position of methoxyl substitution in **Region** □, compound **42** showed an extraordinary anti-tumor activity against HT29 with IC_{50} value of 0.32 μM (As shown in **Figure 2A**), 3 fold than that of **32** and 31 fold than positive drugs(Cisplatin: IC_{50}= 10.75 μM, 5-Fluorouracil: IC_{50}= 13.37 μM).

Moreover, we analysed the toxicity of compound **42** against the human non-tumor liver cell line (LO2) by MTT assay. The results shown in **Figure 2B**, revealed that the cytotoxicity of compound **42** was significantly lower than that of positive drugs Cisplatin and 5-Fluorouracil, thus proving a good in *vitro* safety for compound **42**.

2.3 Inhibition of compounds with c-Myc/MAX dimerization and DNA complex

To identified interaction of synthetic compounds and c-Myc/MAX dimerization was determined by Enzyme-Linked Immunosorbent Assay (ELISA)[37, 59]. The c-Myc/MAX inhibitor sAJM589[60] was used as positive control in ELISA test. As shown in **Table 2**, molecules with R5 group bearing aliphatic alkylamine analogues caused poor inhibition of c-Myc/MAX dimerization, suggesting that the substitutions of R5 group were worthy of further optimization. Subsequent efforts were focused on the substitutions of aromatic analogues of R5 group. Compared with compound **32** substituted with a 2-(4-methoxyphenyl)ethan-1-amine of R5 group showed a dramatic increase inhibitory activity of c-Myc/MAX dimerization. The reason may be that when 2-(4-methoxyphenyl)ethan-1-amine introduced into the molecule, which enhanced hydrophobic interactions of c-Myc/MAX dimerization. Next, we continued to modify the relative position 1,3 to 1,4 within **Region** □, compound **42** showed increased inhibitory potency when compared to that of compound **32**. Among all the molecules, compound **42** showed significant inhibitory activity of c-Myc/MAX dimerization with an IC_{50} value of 63 μM, and positive agent sAJM589 with an IC_{50} value of 36 μM.

In addition, compounds interfered with c-Myc/Max/DNA binding behavior was identified by Electrophoretic Mobility-Shift Assay (EMSA)[37, 56, 61, 62]. As shown in **Table 3**, the different binding inhibition rates were displayed, DMSO as a vehicle control, and among these molecules, compound **42** was demonstrated excellent potent disruption activity of the c-Myc/Max/DNA complex. In **Figrue S1**(Supporting Information, **Figure S1**), the data showed compound **42** could interfered with c-Myc/Max binding DNA in a concentration-dependent manner, when the concentration of **42** was increased to 40 μM, almost complete inhibition of c-Myc/Max/DNA binding.

2.4 Molecular docking study

To further investigate the possible binding mode of **42** with c-Myc/Max, the protein crystal structure of Myc/Max (PDB ID:1NKP)[28] was used in this study. As illustrated in **Figure 3**, the

predicted binding mode and the detailed interaction of compound **42** with Myc/Max were elucidated. Compound **42** could tightly bind to the basic/helix-loop-helix/leucine zipper (bHLHZ) domains of Myc-Max. It was clearly seen that NH in N-phenylaniline (**Region** □) segment and Ala237 formed hydrogen bond, and N-phenylaniline interacted with ILe242, arg226, His223 via hydrophobic features, respectively. Besides, two methoxy groups of **Region** □ segment interacted with Arg913 by hydrogen bond. More importantly, NH in **Region** □ segment and Arg913 formed an additional hydrogen bond. Furthermore, the phenyl group in **Region** □ among Lys939, Lys918, Arg914 formed hydrophobic interaction, respectively. Additionally, the whole molecule located in Myc-Max dimer interface and protein-DNA interface, which indicated that the binding stability of the molecule and Myc-Max proteins that could disrupt c-Myc/Max/DNA complex formation. All characteristics of molecular binding mode could prefigure the significant cytotoxicity activity of compound **42**.

2.5. Colony formation assay of compound **42**

Plate clone formation test[61] of compound **42** was indicated in **Figure 4**, HT29 cells and HCT15 cells were treated with compound **42**, then incubated overnight at 37 ^{o}C for 15days. The colony formation rate of HCT15 cells and HT29 cells decreased dramatically in the treatment groups. It can be appreciated in **Figure 4**, that when the concentration of **42** was increased to 1.25 μM, almost no colony formation was observed in HT29 cells. Similarity, when the concentration of **42** reached 2.5 μM in HCT15 cells, almost complete inhibition of colony formation was observed. As was expected, the results of plate colony formation corresponded with the results of MTT assay.

2.6. Flow cytometry of compound **42**.

To investigate the effect of the cell cycle distribution and the cell apoptosis rate by compound **42** HT29 and HCT15 cells were treated at different concentrations of **42** for 24 h[61]. As displayed in **Figure 5A**, cell cycle progression was significantly arrested at G0/G1 phase both in HT29 and HCT15 cells, and the differentiation of the cell cycle distribution was evidently in a dose-dependent manner with compound **42**. The induction of cell cycle arrest inhibited cell proliferation that reflected their capabilities to disrupt binding to the c-Myc/Max/DNA complex.

As represented in **Figure 5B**, **42** was found to significantly affect HT29 and HCT15 cells apoptosis in a dose-dependent manner with different concentration. Compound **42**, at a concentration of 10 μM, causes apoptosis of HT29 and HCT15 cells after 24 h, demonstrating that the inhibition ofc-Myc in proliferating cells was splendid.

2.7. Western blot assay of compound **42**

The ability of **42** to inhibit c-Myc expression was detected by western blot [62]. The results showed that **42** decreased the expression level of c-Myc protein both in HT29 cells and HCT15 cells. As shown in **Figure 6**, it was clearly seen that downregulation of c-Myc protein was achieved in a dose-dependent manner with compound **42**. These results suggest that compound **42** might target the c-Myc/Max in HT29 cells and HCT15 cells, thus presumably down-regulating its expression.

2.8. In *vivo* effects of **42** on HT29 tumor xenograft model

The in *vitro* promising results achieved with compound **42** prompted us to study the in *vivo*[61, 63] activity of this compound. Female BALB/c nude mice (6-7 weeks old) bearing HT29 xenograft tumors were treated with **42** by oral administration for 30 days. As illustrated in **Figure 7**, compound **42** remarkably inhibited tumor growth in a dose-dependent manner. Tumor growth inhibitions (TGIs) of 71.58%, 61.21%, 55.17% were observed in the HT29 xenograft model at dose of 120mg/kg, 80mg/kg, 40mg/kg, respectively. 5-Fluorouracil was used as positive control at dose of 30mg/kg, the mice body weight was significantly reduced after 10 days of treatment. On the contrary, during 30 days treatment with **42** exhibited excellent anti-tumor efficacy without causing significant weight loss and toxicity.

3. CONCLUSIONS

In this investigation, a series of N-phenylaniline derivatives were designed and synthesized, and the in vitro cell viability against CRC lines was evaluated. Among these synthetic molecules, derivative **42** showed good in *vitro* antiproliferative activities against HT29, HCT15, HCT16 with IC50 values of 0.32 μM, 0.51 μM, 0.82 μM, respectively. Additionally, SAR study presented that the junction of Region □ with Region □ to C-4 position, and Region □ connected to N-(2,6-dimethoxybenzyl)-2-(4-methoxyphenyl)ethan-1-amine might make an enormous contribution to the biological activity. Besides, EMSA binding ability test and molecular docking study demonstrated that **42** exhibit an excellent binding affinity to c-Myc/Max via its unique structural features. The target compound **42** showed explicit induced apoptosis for HT29 and HCT15 in a dose-dependent manner, and cell cycle arrest at the G0/G1 phase on HT29 and HCT15 cells. Furthermore, western blot analysis showed down-regulation of the expression of c-Myc in HT29 and HCT15 cells by compound **42**, which could indicate that compound **42** would be inhibiting Myc/MAX interaction. More importantly, we demonstrated that compound **42** revealed eminent antitumor ability in *vivo* on HT29 tumor xenograft model with generating no significant weight loss and toxicity. All of the studies illustrate here support **42** is a promising novel drug candidate for therapy of CRC.

4. EXPERIMENTAL SECTION

4.1 Chemistry. All reagents and solvents were obtained from standard suppliers and used without further purification. Anhydrous solvents were dried and purified by standard chemical reagent purification**.** ^{1}H (400 MHz) and ^{13}C NMR (101 MHz) spectra were recorded on a Bruker AV-400 spectrometer at 25 ^{o}C with $CDCl_3$. Chemical shifts are represented in δ(ppm) values with tetramethylsilane (TMS) as an internal standard. Low-resolution and high-resolution ESI−MS was taken on a Bruker Amjzon mass spectrometer. All reactions were measured by thin-layer chromatography (TLC) under ultraviolet light (254nm or 365nm) and purified by Silica Gel Column Chromatography (300−400 mesh). All the final products were tested by the Waters e2695 HPLC system, the purity of the final compounds was over 95% for biological testing.

Synthesis of 4-fluoro-2,6-dimethoxybenzaldehyde (3). To a solution of 1-fluoro-3,5-dimethoxybenzene **2** (10 g, 64.06 mmol) under argon atmosphere in anhydrous DMF (20 mL) was stirred at 0 ^{o}C for 20 min, $POCl_3$ (11.77 g, 76.87 mmol) was added in 15min, the reaction mixture was stirred at room temperature for 30 min, then heated at 60 ^{o}C for 4 h. The

reaction was completed, allowed to cool to room temperature, poured into ice-water (400 mL).The aqueous phase was adjusted to pH=9-10 by 4N NaOH, extracted with ethyl acetate (2 x 400 mL), combined organic phases and washed with brine, dried over anhydrous $MgSO_4$. The organic layer was removed by rotary evaporation in vacuo, purified by column chromatography to afford 7.35g white solid product. Yield 62.30%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.44 (s, 1H), 6.77 (s, 2H), 3.91 (s, 6H). ESI-MS: mass calcd for $[M + H]^+$ ($C_9H_9FO_3$) 185.05;found m/z, 185.06.

Synthesis of 3-(phenylamino)phenol (5). A mixture of 3-aminophenol **3** (5 g, 45.82 mmol) and bromobenzene (8.63 g, 54.98 mmol), sodium tert-butoxide (1.32 g, 137.46 mmol), BrettPhos Palladacycle (182.78 mg, 0.23 mmol, 0.5 mmol %) under argon atmosphere in anhydrous 1,4-dioxane 25 mL was stirred at 90 ^{o}C for 2 h. The reaction was completed monitored by TLC. The reaction mixture was concentrated in vacuo, added 500 mL water, extracted with ethyl acetate (2 x 400 mL), combined organic phases and washed with brine, dried over anhydrous $MgSO_4$. The organic layer was concentrated in vacuo and purified by silica gel chromatography to afford 4.31 g brown solid. Yield 86.01%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (dd, *J* = 7.0, 1.5 Hz, 1H), 7.25 (s, 1H), 7.14 – 7.06 (m, 3H), 6.95 (dd, *J* = 10.5, 4.2 Hz, 1H), 6.64 – 6.58 (m, 1H), 6.56 (t, *J* = 2.2 Hz, 1H), 6.37 (ddd, *J* = 8.0, 2.3, 0.7 Hz, 1H), 5.68 (s, 1H), 4.71 (s, 1H). ESI-MS: mass calcd for $[M + H]^+$ ($C_{12}H_{11}NO$) 186.08; found m/z, 186.09.

General procedure A for the synthesis of 6a-6d. To a solution of 3-(phenylamino)phenol **5** (3 g, 16.20 mmol) and K_2CO_3 (6.72 g, 48.59 mmol), 4-Fluorobenzaldehyde with different substituents (16.20 mmol) under argon atmosphere in anhydrous DMSO(15 mL) was stirred at 100 ^{o}C for 3 h and monitored by TLC. The reaction was quenched by cold water (100 mL), extracted with DCM, dried over anhydrous $MgSO_4$, concentrated in vacuo to get crude products, and purified by silica gel chromatography to get desired compounds.

2,6-dimethoxy-4-(3-(phenylamino)phenoxy)benzaldehyde (6a). The title compound was prepared from **5** and 4-fluoro-2,6-dimethoxybenzaldehyde following the general procedure of **A**. Yield: 85.21%, brown solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.30 (s, 1H), 7.25 – 7.20 (m, 2H), 7.17 (s, 1H), 7.07 – 7.02 (m, 2H), 6.92 (t, *J* = 7.4 Hz, 1H), 6.80 (ddd, *J* = 8.1, 2.2, 0.8 Hz, 1H), 6.73 (t, *J* = 2.2 Hz, 1H), 6.53 (ddd, *J* = 8.1, 2.3, 0.8 Hz, 1H), 6.10 (s, 2H), 3.74 (s, 6H). ESI-MS: mass calcd for $[M + H]^+$ ($C_{21}H_{19}NO_4$) 350.13; found m/z, 350.23.

2-methoxy-4-(3-(phenylamino)phenoxy)benzaldehyde (6b). The title compound was prepared from **5** and 4-fluoro-2-methoxybenzaldehyde following the general procedure of **A**. Yield: 82.35%, white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.31 (s, 1H), 7.77 (d, *J* = 8.6 Hz, 1H), 7.30 – 7.23 (m, 3H), 7.09 (d, *J* = 7.6 Hz, 2H), 6.96 (t, *J* = 7.4 Hz, 1H), 6.87 (dd, *J* = 8.1, 1.6 Hz, 1H), 6.78 (t, *J* = 2.1 Hz, 1H), 6.62 – 6.52 (m, 3H), 5.90 (s, 1H), 3.85 (s, 3H). ESI-MS: mass calcd for $[M + H]^+$ ($C_{20}H_{17}NO_3$) 320.12; found m/z, 320.13.

3-methoxy-4-(3-(phenylamino)phenoxy)benzaldehyde (6c). The title compound was prepared from **5** and 4-fluoro-3-methoxybenzaldehyde following the general procedure of **A**. Yield: 78.82%, colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.89 (s, 1H), 7.51 (d, *J* = 1.7 Hz, 1H), 7.39 (dd, *J* = 8.2, 1.8 Hz, 1H), 7.29 – 7.22 (m, 3H), 7.08 (d, *J* = 7.8 Hz, 2H), 6.97 (dd, *J* = 15.6, 7.8 Hz, 2H), 6.83 (dd, *J* = 8.1, 2.0 Hz, 1H), 6.77 (t, *J* = 2.1 Hz, 1H), 6.56 (dd, *J* = 8.1, 2.2 Hz, 1H), 3.96 (s, 3H). ESI-MS: mass calcd for $[M + H]^+$ ($C_{20}H_{17}NO_3$) 320.12; found m/z, 320.12.

4-(3-(phenylamino)phenoxy)benzaldehyde (6d). The title compound was prepared from **4** and 4-fluorobenzaldehyde following the general procedure of **A**. Yield: 73.55%, colorless oil. ^{1}H NMR

(400 MHz, $CDCl_3$) δ 9.92 (s, 1H), 7.88 – 7.82 (m, 2H), 7.31 – 7.25 (m, 3H), 7.09 (ddd, *J* = 7.9, 4.8, 1.8 Hz, 4H), 6.97 (dd, *J* = 10.5, 4.2 Hz, 1H), 6.90 – 6.85 (m, 1H), 6.78 (t, *J* = 2.2 Hz, 1H), 6.59 (ddd, *J* = 8.1, 2.2, 0.7 Hz, 1H), 5.79 (s, 1H). ESI-MS: mass calcd for $[M + H]^+$ ($C_{19}H_{15}NO_2$) 290.11; found m/z, 290.12.

General procedure B for the synthesis of 7-38. To a solution of **6(a-d)** (0.30mmol) , sodium triacetoxyborohydride (127 mg, 0.60 mmol), different amines (0.36mmol), added acetic acid (0.03mmol) under argon atmosphere in anhydrous DMF(2 mL) was stirred at 80 ^oC for over night and monitored by TLC. The reaction was quenched by cold water (100 mL), extracted with ethyl acetate, dried over anhydrous $MgSO_4$, concentrated in vacuo to get crude products, and purified by flash column chromatography to get desired compounds.

3-(3,5-dimethoxy-4-((methylamino)methyl)phenoxy)-N-phenylaniline (7). The title compound was prepared from **6a** and methylamine hydrochloride following the general procedure of **B**. Yield: 52.50%, brown solid. ^1H NMR (400 MHz, $CDCl_3$) δ 7.28 (d, *J* = 7.8 Hz, 2H), 7.22 (t, *J* = 8.1 Hz, 1H), 7.10 (d, *J* = 7.9 Hz, 2H), 6.96 (t, *J* = 7.3 Hz, 1H), 6.84 (d, *J* = 8.1 Hz, 1H), 6.73 (s, 1H), 6.56 (d, *J* = 7.9 Hz, 1H), 6.23 (s, 2H), 4.21 (s, 2H), 3.81 (s, 6H), 2.54 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.42, 160.03, 157.26, 145.23, 142.27, 130.47, 129.41, 121.76, 118.68, 112.52, 111.12, 107.78, 101.09, 94.70, 56.01, 40.47, 31.19. ESI-MS: mass calcd for $[M + H]^+$ ($C_{22}H_{24}N_2O_3$) 365.18; found m/z, 365.19. Purity 95.1% by HPLC.

3-(4-((cyclopropylamino)methyl)-3,5-dimethoxyphenoxy)-N-phenylaniline (8). The title compound was prepared from **6a** and cyclopropanamine following the general procedure of **B**. Yield: 61.05%, brown solid. ^1H NMR (400 MHz, $CDCl_3$) δ 7.25 (d, *J* = 7.2 Hz, 2H), 7.19 (t, *J* = 8.1 Hz, 1H), 7.09 (d, *J* = 7.6 Hz, 2H), 6.95 (t, *J* = 7.4 Hz, 1H), 6.80 (dd, *J* = 8.0, 2.0 Hz, 1H), 6.71 (t, *J* = 2.2 Hz, 1H), 6.54 (dd, *J* = 8.1, 2.2 Hz, 1H), 6.26 (s, 2H), 5.81 (s, 1H), 4.02 (s, 2H), 3.77 (s, 6H), 2.20 (tt, *J* = 7.2, 3.7 Hz, 1H), 0.71 (m, 2H), 0.52 (q, *J* = 6.6 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.82, 145.11, 142.36, 130.39, 129.38, 121.64, 118.56, 112.16, 110.77, 107.44, 95.18, 55.92, 40.47, 29.37, 4.40. ESI-MS: mass calcd for $[M + H]^+$ ($C_{24}H_{26}N_2O_3$) 391.19; found m/z, 391.20. Purity 96.7% by HPLC.

3-(4-((isopropylamino)methyl)-3,5-dimethoxyphenoxy)-N-phenylaniline (9). The title compound was prepared from **6a** and propan-2-amine following the general procedure of **B**. Yield: 52.36%, brown solid. ^1H NMR (400 MHz, $CDCl_3$) δ 7.29 (s, 2H), 7.25 (s, 1H), 7.20 (t, *J* = 8.1 Hz, 1H), 7.10 (d, *J* = 7.7 Hz, 2H), 6.95 (t, *J* = 7.3 Hz, 1H), 6.82 (d, *J* = 8.1 Hz, 1H), 6.70 (d, *J* = 2.0 Hz, 1H), 6.55 (dd, *J* = 8.1, 1.7 Hz, 1H), 6.25 (s, 2H), 5.92 (s, 1H), 4.02 (s, 2H), 3.77 (s, 6H), 2.95 (dt, *J* = 12.9, 6.4 Hz, 1H), 1.23 (d, *J* = 6.4 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.57, 157.93, 145.09, 142.36, 130.38, 129.38, 121.64, 118.55, 112.05, 110.67, 107.33, 95.42, 55.88, 46.94, 40.29, 37.81, 23.17. ESI-MS: mass calcd for $[M + H]^+$ ($C_{24}H_{28}N_2O_3$) 393.21; found m/z, 393.21. Purity 98.1% by HPLC.

3-*(4-((dimethylamino)methyl)-3,5-dimethoxyphenoxy)-N-phenylaniline (10).* The title compound was prepared from **6a** and dimethylamine following the general procedure of **B**. Yield: 45.77%, brown solid. ^1H NMR (400 MHz, $CDCl_3$) δ 7.31 – 7.27 (m, 2H), 7.23 (d, *J* = 8.1 Hz, 1H), 7.11 (d, *J* = 7.6 Hz, 2H), 6.97 (t, *J* = 7.3 Hz, 1H), 6.86 (dd, *J* = 8.1, 1.9 Hz, 1H), 6.76 (t, *J* = 2.2 Hz, 1H), 6.58 (dd, *J* = 8.0, 2.1 Hz, 1H), 6.25 (s, 2H), 5.89 (s, 1H), 4.22 (s, 2H), 3.81 (s, 6H), 2.72 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.35, 160.49, 156.76, 145.32, 142.18, 130.58, 129.43, 121.90, 118.78, 112.95, 111.44, 108.02, 99.54, 94.50, 56.04, 49.03, 42.40, 29.70. ESI-MS:

mass calcd for $[M + H]^+$ ($C_{23}H_{26}N_2O_3$) 379.19; found m/z, 379.20. Purity 95.3% by HPLC.

2,2'-((2,6-dimethoxy-4-(3-(phenylamino)phenoxy)benzyl)azanediyl)bis(ethan-1-ol) (11). The title compound was prepared from **6a** and 2,2'-azanediylbis(ethan-1-ol) following the general procedure of **B**. Yield: 56.15%, yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (d, *J* = 7.8 Hz, 1H), 7.23 (d, *J* = 8.1 Hz, 1H), 7.11 (d, *J* = 7.9 Hz, 1H), 6.97 (t, *J* = 7.3 Hz, 1H), 6.86 (dd, *J* = 8.2, 1.5 Hz, 1H), 6.76 (s, 1H), 6.58 (dd, *J* = 7.9, 1.6 Hz, 1H), 6.25 (s, 1H), 5.88 (s, 1H), 4.35 (s, 1H), 3.99 (s, 2H), 3.81 (s, 3H), 3.28 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.02, 130.58, 129.41, 121.84, 118.76, 112.88, 111.44, 108.05, 94.65, 56.15, 56.10, 55.35, 47.58. ESI-MS: mass calcd for $[M + H]^+$ ($C_{25}H_{30}N_2O_5$) 439.22; found m/z, 439.23. Purity 97.2% by HPLC.

N-(2-((2,6-dimethoxy-4-(3-(phenylamino)phenoxy)benzyl)amino)ethyl)acetamide (12). The title compound was prepared from **6a** and N-(2-aminoethyl)acetamide following the general procedure of **B**. Yield: 61.42 %, brown oil.^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (d, *J* = 7.0 Hz, 2H), 7.20 (t, *J* = 8.1 Hz, 1H), 7.13 – 7.08 (m, 2H), 7.00 (s, 1H), 6.94 (t, *J* = 7.3 Hz, 1H), 6.83 (dd, *J* = 8.1, 1.5 Hz, 1H), 6.64 (t, *J* = 2.2 Hz, 1H), 6.55 (dd, *J* = 8.1, 1.6 Hz, 1H), 6.26 (s, 2H), 6.08 (s, 1H), 3.92 (s, 2H), 3.77 (s, 6H), 3.39 (d, *J* = 5.3 Hz, 2H), 2.84 – 2.73 (m, 2H), 1.97 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.65, 159.51, 158.60, 158.02, 145.15, 142.43, 130.37, 129.36, 121.57, 118.51, 111.85, 110.59, 107.22, 95.44, 55.88, 46.94, 40.29, 37.81, 23.17. ESI-MS: mass calcd for $[M + H]^+$ ($C_{25}H_{29}N_3O_4$) 436.22; found m/z, 436.23. Purity 98.1% by HPLC.

2-(4-(2,6-dimethoxy-4-(3-(phenylamino)phenoxy)benzyl)piperazin-1-yl)ethan-1-ol (13). The title compound was prepared from **6a** and 2-(piperazin-1-yl)ethan-1-ol following the general procedure of **B**. Yield: 53.18%, brown oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (dd, *J* = 7.0, 1.4 Hz, 2H), 7.23 (t, *J* = 8.1 Hz, 1H), 7.14 – 7.08 (m, 2H), 6.96 (t, *J* = 7.4 Hz, 1H), 6.84 (dd, *J* = 8.1, 1.5 Hz, 1H), 6.75 (t, *J* = 2.2 Hz, 1H), 6.57 (dd, *J* = 8.1, 1.6 Hz, 1H), 6.25 (s, 2H), 5.88 (s, 1H), 4.08 (s, 2H), 3.76 (s, 6H), 3.70 – 3.65 (m, 2H), 2.93 (s, 7H), 2.72 – 2.66 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.54, 157.23, 145.23, 142.25, 130.49, 129.41, 121.81, 118.69, 112.62, 111.18, 107.79, 99.99, 94.89, 59.16, 57.64, 55.93, 50.55, 48.17. ESI-MS: mass calcd for $[M + H]^+$ ($C_{27}H_{33}N_3O_4$) 464.25; found m/z, 464.26. Purity 96.5% by HPLC.

3-(4-((4-ethylpiperazin-1-yl)methyl)-3,5-dimethoxyphenoxy)-N-phenylaniline (14). The title compound was prepared from **6a** and 1-ethylpiperazine following the general procedure of **B**. Yield: 62.33%, brown solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (s, 1H), 7.25 (s, 1H), 7.20 (t, *J* = 8.1 Hz, 1H), 7.10 (d, *J* = 8.0 Hz, 2H), 6.95 (t, *J* = 7.3 Hz, 1H), 6.81 (d, *J* = 8.1 Hz, 1H), 6.71 (s, 1H), 6.55 (dd, *J* = 8.1, 1.9 Hz, 1H), 6.24 (s, 2H), 5.88 (s, 1H), 3.84 (s, 2H), 3.73 (s, 6H), 2.72 (d, *J* = 46.0 Hz, 8H), 2.50 – 2.44 (m, 2H), 1.10 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.30, 158.01, 145.04, 142.40, 130.34, 129.38, 121.61, 118.55, 112.07, 110.73, 107.38, 95.41, 55.82, 52.10, 51.92, 51.50, 48.48, 11.67. ESI-MS: mass calcd for $[M + H]^+$ ($C_{27}H_{33}N_3O_3$) 448.25; found m/z, 448.25. Purity 95.4% by HPLC.

(1s,3s)-N-(2,6-dimethoxy-4-(3-(phenylamino)phenoxy)benzyl)adamantan-1-amine (15). The title compound was prepared from **6a** and amantadine following the general procedure of **B**. Yield: 41.27%, yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (s, 1H), 7.24 (s, 1H), 7.21 (d, *J* = 8.1 Hz, 1H), 7.12 (d, *J* = 7.7 Hz, 2H), 6.94 (t, *J* = 7.3 Hz, 1H), 6.85 (d, *J* = 8.1 Hz, 1H), 6.69 (s, 1H), 6.55 (dd, *J* = 8.0, 1.6 Hz, 1H), 6.23 (d, *J* = 8.1 Hz, 2H), 4.16 (s, 2H), 3.82 (s, 6H), 2.13 (s, 3H), 2.00 (s, 6H), 1.64 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.91, 159.42, 157.66, 145.22, 142.36, 130.38, 129.34, 121.57, 118.62, 111.91, 110.82, 107.57, 102.98, 95.45, 58.30, 56.16, 38.68, 35.58, 33.64, 29.11. ESI-MS: mass calcd for $[M + H]^+$ ($C_{31}H_{36}N_2O_3$) 485.27; found m/z, 485.28. Purity 97.3%

by HPLC.

(2,6-dimethoxy-4-(3-(phenylamino)phenoxy)phenyl)methanol (16). The title compound was prepared from **6a** (50 mg, 0.142mmol) and $NaBH_4$ (2 mg, 0.057 mmol) stirred in MeOH at room room temperature for 2min. The reaction was concentrated in vacuo to get crude products, and purified by silica gel chromatography to get **35**. Yield: 65.25 %, colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 – 7.24 (m, 2H), 7.19 (t, *J* = 8.1 Hz, 1H), 7.08 (d, *J* = 7.6 Hz, 2H), 6.96 (d, *J* = 7.3 Hz, 1H), 6.79 (dd, *J* = 8.0, 1.9 Hz, 1H), 6.72 (t, *J* = 2.2 Hz, 1H), 6.54 (dd, *J* = 8.1, 1.8 Hz, 1H), 6.26 (s, 2H), 5.78 (s, 1H), 4.73 (s, 2H), 3.77 (s, 6H). ESI-MS: mass calcd for $[M + H]^+$ ($C_{21}H_{21}NO_4$) 352.15; found m/z, 352.16. Purity 96.9% by HPLC.

3-(4-((benzylamino)methyl)-3,5-dimethoxyphenoxy)-N-phenylaniline (17). The title compound was prepared from **6a** and phenylmethanamine following the general procedure of **B**. Yield: 58.02%, brown solid.^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (dt, *J* = 9.7, 4.2 Hz, 5H), 7.23 (d, *J* = 6.4 Hz, 2H), 7.19 (t, *J* = 8.1 Hz, 1H), 7.08 (d, *J* = 7.8 Hz, 2H), 6.94 (t, *J* = 7.3 Hz, 1H), 6.78 (dd, *J* = 8.0, 1.6 Hz, 1H), 6.72 (t, *J* = 2.1 Hz, 1H), 6.54 (dd, *J* = 8.1, 2.0 Hz, 1H), 6.26 (s, 2H), 5.75 (s, 1H), 3.84 (s, 2H), 3.76 (s, 2H), 3.73 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.45, 158.45, 157.27, 144.94, 142.43, 140.86, 130.30, 129.39, 128.20, 126.67, 121.62, 118.50, 111.91, 111.74, 110.49, 107.19, 95.62, 55.73, 53.12, 41.05. ESI-MS: mass calcd for $[M + H]^+$ ($C_{28}H_{28}N_2O_3$) 441.21; found m/z, 441.21. Purity 95.6% by HPLC.

3-(4-(((4-fluorobenzyl)amino)methyl)-3,5-dimethoxyphenoxy)-N-phenylaniline (18). The title compound was prepared from **6a** and (4-fluorophenyl)methanamine following the general procedure of **B**. Yield: 53.72%, yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 – 7.23 (m, 4H), 7.18 (t, *J* = 8.1 Hz, 1H), 7.07 (d, *J* = 7.7 Hz, 2H), 7.02 – 6.91 (m, 3H), 6.77 (dd, *J* = 8.1, 1.4 Hz, 1H), 6.71 (t, *J* = 2.0 Hz, 1H), 6.53 (dd, *J* = 8.1, 1.7 Hz, 1H), 6.25 (s, 2H), 5.80 (s, 1H), 3.82 (s, 2H), 3.72 (s, 8H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.03, 160.61, 159.44, 158.39, 157.37, 144.99, 142.46, 136.61, 136.58, 130.32, 129.75, 129.67, 129.59, 129.39, 121.60, 121.25, 118.50, 115.01, 114.80, 111.97, 111.59, 110.50, 107.23, 95.59, 55.73, 52.33, 40.92. ESI-MS: mass calcd for $[M + H]^+$ ($C_{28}H_{27}FN_2O_3$) 459.20; found m/z, 459.21. Purity 98.1% by HPLC.

3-(4-(((4-chlorobenzyl)amino)methyl)-3,5-dimethoxyphenoxy)-N-phenylaniline (19). The title compound was prepared from **6a** and (4-chlorophenyl)methanamine following the general procedure of **B**. Yield: 58.87%, brown solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 – 7.22 (m, 6H), 7.19 (d, *J* = 8.1 Hz, 1H), 7.10 – 7.05 (m, 2H), 6.93 (t, *J* = 7.4 Hz, 1H), 6.80 – 6.75 (m, 1H), 6.71 (t, *J* = 2.2 Hz, 1H), 6.56 – 6.51 (m, 1H), 6.25 (s, 2H), 5.80 (s, 1H), 3.81 (s, 2H), 3.72 (s, 8H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.44, 158.34, 157.46, 144.99, 142.45, 139.26, 132.34, 130.33, 129.58, 129.39, 128.28, 121.61, 118.51, 112.01, 111.35, 110.53, 107.26, 95.54, 55.73, 52.25, 40.86. ESI-MS: mass calcd for $[M + H]^+$ ($C_{28}H_{27}ClN_2O_3$) 475.17; found m/z, 475.17. Purity 97.1% by HPLC.

3-(4-(((4-bromobenzyl)amino)methyl)-3,5-dimethoxyphenoxy)-N-phenylaniline (20). The title compound was prepared from **6a** and (4-bromophenyl)methanamine following the general procedure of **B**. Yield: 61.25%, brown solid.^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (d, *J* = 8.3 Hz, 2H), 7.26 – 7.17 (m, 5H), 7.08 (d, *J* = 7.6 Hz, 2H), 6.94 (t, *J* = 7.4 Hz, 1H), 6.80 – 6.76 (m, 1H), 6.72 (t, *J* = 2.2 Hz, 1H), 6.56 – 6.52 (m, 1H), 6.25 (s, 2H), 5.77 (s, 1H), 3.81 (s, 2H), 3.72 (d, *J* = 6.5 Hz, 8H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.43, 158.33, 157.46, 144.97, 142.44, 139.79, 131.23, 130.33, 129.96, 129.39, 121.63, 120.42, 118.51, 112.01, 111.35, 110.55, 107.26, 95.54, 55.73, 52.28, 40.85. ESI-MS: mass calcd for $[M + H]^+$ ($C_{28}H_{27}BrN_2O_3$) 519.12, 521.12; found m/z,

519.13, 521.13 . Purity 96.8% by HPLC.

4-(((2,6-dimethoxy-4-(3-(phenylamino)phenoxy)benzyl)amino)methyl)phenol (21). The title compound was prepared from **6a** and 4-(aminomethyl)phenol following the general procedure of **B**. Yield: 48.73%, brown oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 – 7.22 (m, 2H), 7.18 (t, *J* = 8.1 Hz, 1H), 7.07 (dd, *J* = 8.5, 1.0 Hz, 2H), 7.02 (d, *J* = 8.4 Hz, 2H), 6.93 (t, *J* = 7.3 Hz, 1H), 6.81 – 6.77 (m, 1H), 6.69 (t, *J* = 2.2 Hz, 1H), 6.58 – 6.51 (m, 3H), 6.23 (s, 2H), 5.84 (s, 1H), 3.89 (s, 2H), 3.70 (s, 6H), 3.62 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.46, 158.21, 157.75, 156.24, 145.01, 142.45, 130.33, 129.97, 129.71, 129.37, 121.60, 118.51, 115.76, 111.97, 110.61, 110.16, 107.34, 95.46, 55.74, 52.09, 40.74. ESI-MS: mass calcd for $[M + H]^+$ ($C_{28}H_{28}N_2O_4$) 457.20; found m/z, 457.21. Purity 97.3% by HPLC.

3-(3,5-dimethoxy-4-(((4-methoxybenzyl)amino)methyl)phenoxy)-N-phenylaniline (22). The title compound was prepared from **6a** and (4-methoxyphenyl)methanamine following the general procedure of **B**. Yield: 55.61%, brown solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (d, *J* = 8.5 Hz, 2H), 7.26 (s, 2H), 7.20 (t, *J* = 8.1 Hz, 1H), 7.10 (d, *J* = 7.7 Hz, 2H), 6.95 (t, *J* = 7.3 Hz, 1H), 6.88 – 6.83 (m, 3H), 6.66 (t, *J* = 2.1 Hz, 1H), 6.53 (dd, *J* = 8.0, 1.9 Hz, 1H), 6.20 (s, 2H), 5.98 (s, 1H), 4.07 (s, 2H), 3.91 (s, 2H), 3.77 (s, 3H), 3.73 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.85, 159.65, 157.58, 145.19, 142.35, 131.06, 130.41, 129.39, 124.88, 121.68, 118.60, 114.11, 112.13, 110.86, 107.53, 95.06, 55.90, 55.29, 49.65, 39.00. ESI-MS: mass calcd for $[M + H]^+$ ($C_{29}H_{30}N_2O_4$) 471.22; found m/z, 471.22. Purity 96.2% by HPLC.

3-(3,5-dimethoxy-4-(((4-methylbenzyl)amino)methyl)phenoxy)-N-phenylaniline (23). The title compound was prepared from **6a** and p-tolylmethanamine following the general procedure of **B**. Yield: 52.72%, brown solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 – 7.18 (m, 2H), 7.15 (dd, *J* = 10.1, 3.5 Hz, 3H), 7.11 (t, *J* = 8.1 Hz, 1H), 7.04 (d, *J* = 7.9 Hz, 2H), 7.01 (dd, *J* = 8.5, 1.0 Hz, 2H), 6.86 (dd, *J* = 10.5, 4.2 Hz, 1H), 6.72 (dd, *J* = 8.1, 1.5 Hz, 1H), 6.64 (t, *J* = 2.2 Hz, 1H), 6.48 – 6.44 (m, 1H), 6.17 (s, 2H), 5.74 (s, 1H), 3.80 (s, 2H), 3.68 (s, 2H), 3.65 (s, 6H), 2.25 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.49, 158.27, 157.70, 145.00, 142.43, 136.62, 136.36, 130.31, 129.38, 129.00, 128.39, 121.61, 118.52, 111.97, 110.55, 110.29, 107.28, 95.50, 55.75, 52.35, 40.73, 21.11. ESI-MS: mass calcd for $[M + H]^+$ ($C_{29}H_{30}N_2O_3$) 455.23; found m/z, 455.24. Purity 98.6% by HPLC.

3-(4-(((benzo[d][1,3]dioxol-5-ylmethyl)amino)methyl)-3,5-dimethoxyphenoxy)-N-phenylaniline (24). The title compound was prepared from **6a** and benzo[d][1,3]dioxol-5-ylmethanamine following the general procedure of **B**. Yield: 58.36%, brown solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (d, *J* = 8.5 Hz, 2H), 7.20 (t, *J* = 8.1 Hz, 1H), 7.10 (d, *J* = 7.6 Hz, 2H), 6.99 (s, 1H), 6.95 (t, *J* = 7.4 Hz, 1H), 6.90 (d, *J* = 7.9 Hz, 1H), 6.84 (dd, *J* = 8.1, 1.6 Hz, 1H), 6.74 (d, *J* = 7.9 Hz, 1H), 6.67 (t, *J* = 2.2 Hz, 1H), 6.52 (dd, *J* = 8.0, 1.7 Hz, 1H), 6.19 (s, 2H), 5.92 (s, 2H), 4.09 (s, 2H), 3.90 (s, 2H), 3.75 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.08, 159.67, 157.35, 148.17, 147.94, 145.21, 142.31, 130.44, 129.41, 125.31, 123.86, 121.74, 118.64, 112.32, 111.01, 110.18, 108.43, 107.69, 102.21, 101.31, 94.87, 55.95, 49.76, 38.85. ESI-MS: mass calcd for $[M + H]^+$ ($C_{29}H_{28}N_2O_5$) 485.20; found m/z, 485.20. Purity 95.4% by HPLC.

(R)-3-(3,5-dimethoxy-4-(((1-phenylethyl)amino)methyl)phenoxy)-N-phenylaniline (25). The title compound was prepared from **6a** and (R)-1-phenylethan-1-amine following the general procedure of **B**. Yield: 51.83 %, brown solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 – 7.45 (m, 2H), 7.32 (ddd, *J* = 9.4, 6.6, 1.9 Hz, 4H), 7.24 (t, *J* = 1.9 Hz, 1H), 7.17 (t, *J* = 8.1 Hz, 1H), 7.09 (dd, *J* = 8.5, 1.0 Hz, 2H), 6.95 (t, *J* = 7.3 Hz, 1H), 6.81 (dd, *J* = 8.1, 1.5 Hz, 1H), 6.67 (t, *J* = 2.2 Hz, 1H), 6.50 (dd, *J* =

8.1, 1.6 Hz, 1H), 6.16 (s, 2H), 5.92 (s, 1H), 3.98 (d, *J* = 6.7 Hz, 1H), 3.97 – 3.92 (m, 2H), 3.71 (s, 6H), 1.64 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.64, 159.27, 157.75, 145.10, 142.40, 130.33, 129.39, 128.70, 128.30, 127.57, 121.62, 118.54, 112.10, 110.75, 107.49, 95.04, 57.98, 55.80, 38.52, 21.10. ESI-MS: mass calcd for $[M + H]^+$ ($C_{29}H_{30}N_2O_3$) 455.23; found m/z, 455.23. Purity 97.7% by HPLC.

(R)-3-(3,5-dimethoxy-4-(((1-(4-methoxyphenyl)ethyl)amino)methyl)phenoxy)-N-phenylaniline (26). The title compound was prepared from **6a** and (R)-1-(4-methoxyphenyl)ethan-1-amine following the general procedure of **B**. Yield: 50.07 %, brown solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 – 7.25 (m, 4H), 7.18 (t, *J* = 8.1 Hz, 1H), 7.09 (d, *J* = 7.7 Hz, 2H), 6.94 (t, *J* = 7.3 Hz, 1H), 6.86 (d, *J* = 8.6 Hz, 2H), 6.79 (dd, *J* = 8.1, 1.4 Hz, 1H), 6.69 (t, *J* = 2.1 Hz, 1H), 6.53 (dd, *J* = 8.1, 1.6 Hz, 1H), 6.23 (s, 2H), 5.79 (s, 1H), 3.80 (s, 3H), 3.71 (s, 6H), 3.69 (s, 2H), 1.34 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.40, 158.47, 158.46, 157.24, 144.94, 142.46, 130.28, 129.38, 127.86, 121.59, 118.49, 113.57, 111.81, 110.47, 107.16, 95.65, 56.83, 55.68, 55.28, 39.50, 24.26. ESI-MS: mass calcd for $[M + H]^+$ ($C_{30}H_{32}N_2O_4$) 485.24; found m/z, 485.25. Purity 98.3% by HPLC.

***3-(3,5-dimethoxy-4-((phenethylamino)methyl)phenoxy)-N-phenylaniline (27)*.** The title compound was prepared from **6a** and 2-phenylethan-1-amine following the general procedure of **B**. Yield: 61.09%, brown solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (d, *J* = 4.6 Hz, 3H), 7.22 (dd, *J* = 7.6, 2.9 Hz, 2H), 7.17 – 7.12 (m, 2H), 7.09 (d, *J* = 7.6 Hz, 2H), 6.96 (t, *J* = 7.4 Hz, 1H), 6.83 (dd, *J* = 8.1, 1.5 Hz, 1H), 6.71 (t, *J* = 2.2 Hz, 1H), 6.53 (dd, *J* = 8.1, 1.7 Hz, 1H), 6.18 (s, 2H), 5.85 (s, 1H), 4.19 (s, 2H), 3.65 (s, 6H), 3.11 (d, *J* = 6.2 Hz, 2H), 3.06 (d, *J* = 6.2 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.92, 159.62, 157.36, 145.21, 142.24, 136.87, 130.48, 129.42, 128.92, 128.90, 127.05, 121.83, 118.69, 112.52, 110.96, 107.59, 94.94, 55.88, 47.27, 40.17, 32.62. ESI-MS: mass calcd for $[M + H]^+$ ($C_{29}H_{30}N_2O_3$) 455.23; found m/z, 455.24. Purity 96.5% by HPLC.

***3-(4-(((4-chlorophenethyl)amino)methyl)-3,5-dimethoxyphenoxy)-N-phenylaniline (28)*.** The title compound was prepared from **6a** and 2-(4-chlorophenyl)ethan-1-amine following the general procedure of **B**. Yield: 53.57%, brown solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (s, 2H), 7.25 (d, *J* = 2.5 Hz, 2H), 7.21 (d, *J* = 8.1 Hz, 1H), 7.09 (dd, *J* = 7.5, 5.3 Hz, 4H), 6.96 (t, *J* = 7.3 Hz, 1H), 6.83 (dd, *J* = 8.1, 2.1 Hz, 1H), 6.71 (t, *J* = 2.1 Hz, 1H), 6.53 (dd, *J* = 8.1, 2.2 Hz, 1H), 6.19 (s, 2H), 5.86 (s, 1H), 4.17 (s, 2H), 3.67 (s, 6H), 3.07 (d, *J* = 6.4 Hz, 2H), 3.02 (d, *J* = 6.4 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.43, 159.67, 157.11, 145.27, 142.19, 134.94, 133.15, 130.55, 130.30, 129.44, 129.10, 121.89, 112.72, 111.03, 107.69, 94.81, 55.95, 46.78, 40.05, 31.53. ESI-MS: mass calcd for $[M + H]^+$ ($C_{29}H_{29}ClN_2O_3$) 489.19; found m/z, 489.20. Purity 98.5% by HPLC.

***3-(4-(((4-fluorophenethyl)amino)methyl)-3,5-dimethoxyphenoxy)-N-phenylaniline (29)*.** The title compound was prepared from **6a** and 2-(4-fluorophenyl)ethan-1-amine following the general procedure of **B**. Yield: 48.28%, yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (t, *J* = 7.9 Hz, 2H), 7.20 – 7.06 (m, 5H), 6.99 – 6.90 (m, 3H), 6.77 (dd, *J* = 8.0, 1.5 Hz, 1H), 6.70 (t, *J* = 2.0 Hz, 1H), 6.52 (dd, *J* = 8.1, 1.7 Hz, 1H), 6.23 (s, 2H), 5.81 (s, 1H), 3.81 (s, 2H), 3.67 (s, 6H), 2.80 (dd, *J* = 11.0, 5.3 Hz, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.60, 160.18, 159.34, 158.41, 157.28, 144.98, 142.46, 136.02, 135.99, 130.30, 130.14, 130.07, 129.38, 121.59, 118.49, 115.12, 114.92, 111.94, 111.39, 110.42, 107.17, 95.56, 55.66, 50.15, 41.15, 35.31. ESI-MS: mass calcd for $[M + H]^+$ ($C_{29}H_{29}FN_2O_3$) 473.22; found m/z, 473.23. Purity 97.1% by HPLC.

***3-(3,5-dimethoxy-4-(((4-methylphenethyl)amino)methyl)phenoxy)-N-phenylaniline (30)*.** The

title compound was prepared from **6a** and 2-(p-tolyl)ethan-1-amine following the general procedure of **B**. Yield: 55.37%, yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (s, 1H), 7.23 (d, *J* = 5.4 Hz, 1H), 7.17 (t, *J* = 8.1 Hz, 1H), 7.10 – 7.03 (m, 6H), 6.93 (t, *J* = 7.3 Hz, 1H), 6.77 (dd, *J* = 8.0, 1.6 Hz, 1H), 6.70 (t, *J* = 2.2 Hz, 1H), 6.52 (dd, *J* = 8.1, 1.8 Hz, 1H), 6.22 (s, 2H), 5.89 (s, 1H), 3.86 (s, 2H), 3.65 (s, 6H), 2.83 (dd, *J* = 10.6, 5.3 Hz, 4H), 2.29 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.43, 158.29, 157.67, 145.06, 142.48, 136.73, 135.53, 130.31, 129.38, 129.09, 128.68, 121.58, 118.52, 111.98, 110.47, 110.08, 107.24, 95.47, 55.68, 49.79, 40.94, 35.14, 21.02. ESI-MS: mass calcd for $[M + H]^+$ ($C_{30}H_{32}N_2O_3$) 469.24; found m/z, 469.25. Purity 97.4% by HPLC.

4-(2-((2,6-dimethoxy-4-(3-(phenylamino)phenoxy)benzyl)amino)ethyl)phenol (31). The title compound was prepared from **6a** and 4-(2-aminoethyl)phenol following the general procedure of **B**. Yield: 51.03 %, brown oil. ^{1}H NMR (400 MHz, MeOD) δ 7.21 (td, *J* = 8.2, 4.6 Hz, 3H), 7.11 – 7.04 (m, 4H), 6.89 – 6.84 (m, 2H), 6.77 (s, 1H), 6.74 (dd, *J* = 4.4, 2.2 Hz, 2H), 6.51 – 6.47 (m, 1H), 6.36 (s, 2H), 4.21 (s, 2H), 3.79 (s, 6H), 3.17 – 3.12 (m, 2H), 2.94 – 2.87 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.12, 163.81, 160.91, 160.36, 150.01, 146.90, 134.04, 133.31, 132.73, 130.79, 124.57, 121.86, 119.31, 116.20, 114.04, 110.78, 105.23, 98.17, 59.12, 43.41, 34.69. ESI-MS: mass calcd for $[M + H]^+$ ($C_{29}H_{30}N_2O_4$) 471.22; found m/z, 471.23. Purity 95.8% by HPLC.

3-(3,5-dimethoxy-4-(((4-methoxyphenethyl)amino)methyl)phenoxy)-N-phenylaniline (32). The title compound was prepared from **6a** and 2-(4-methoxyphenyl)ethan-1-amine following the general procedure of **B**. Yield: 58.95 %, brown solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (t, *J* = 7.9 Hz, 2H), 7.18 (t, *J* = 8.1 Hz, 1H), 7.08 (dd, *J* = 8.5, 2.1 Hz, 4H), 6.94 (t, *J* = 7.3 Hz, 1H), 6.85 – 6.76 (m, 3H), 6.70 (d, *J* = 1.9 Hz, 1H), 6.52 (dd, *J* = 8.1, 2.1 Hz, 1H), 6.22 (s, 2H), 5.85 (s, 1H), 3.84 (s, 2H), 3.77 (s, 3H), 3.67 (s, 6H), 2.83 (d, *J* = 5.8 Hz, 2H), 2.79 (d, *J* = 6.0 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.25, 159.73, 158.67, 157.23, 145.26, 142.26, 130.48, 129.92, 129.41, 128.46, 121.78, 118.68, 114.29, 112.52, 111.00, 107.67, 101.40, 94.81, 55.91, 55.29, 47.02, 39.72, 31.23. ESI-MS: mass calcd for $[M + H]^+$ ($C_{30}H_{32}N_2O_4$) 485.24; found m/z, 484.25. Purity 96.9% by HPLC.

3-(3,5-dimethoxy-4-(((2-methoxyphenethyl)amino)methyl)phenoxy)-N-phenylaniline (33). The title compound was prepared from **6a** and 2-(2-methoxyphenyl)ethan-1-amine following the general procedure of **B**. Yield: 47.64 %, brown solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (t, *J* = 7.9 Hz, 2H), 7.20 – 7.11 (m, 3H), 7.08 (d, *J* = 7.6 Hz, 2H), 6.94 (t, *J* = 7.3 Hz, 1H), 6.88 – 6.76 (m, 3H), 6.70 (t, *J* = 2.1 Hz, 1H), 6.51 (dd, *J* = 8.1, 1.7 Hz, 1H), 6.22 (s, 2H), 5.83 (s, 1H), 3.87 (s, 2H), 3.75 (s, 3H), 3.67 (s, 6H), 2.87 (s, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.40, 158.37, 157.68, 157.45, 145.01, 142.45, 130.42, 130.29, 129.38, 128.29, 127.38, 121.59, 120.40, 118.52, 111.92, 110.40, 110.38, 107.17, 95.52, 55.70, 55.26, 48.33, 41.06, 30.36. ESI-MS: mass calcd for $[M + H]^+$ ($C_{30}H_{32}N_2O_4$) 485.24; found m/z, 484.25. Purity 97.5% by HPLC.

3-(3,5-dimethoxy-4-(((3-methoxyphenethyl)amino)methyl)phenoxy)-N-phenylaniline (34). The title compound was prepared from **6a** and 2-(3-methoxyphenyl)ethan-1-amine following the general procedure of **B**. Yield: 52.11 %, brown solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (t, *J* = 7.9 Hz, 2H), 7.17 (t, *J* = 8.0 Hz, 2H), 7.07 (d, *J* = 7.7 Hz, 2H), 6.93 (t, *J* = 7.3 Hz, 1H), 6.81 – 6.67 (m, 5H), 6.52 (dd, *J* = 8.1, 1.8 Hz, 1H), 6.22 (s, 2H), 5.87 (s, 1H), 3.83 (s, 2H), 3.76 (s, 3H), 3.66 (s, 6H), 2.83 (dd, *J* = 15.7, 5.8 Hz, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.68, 159.38, 158.42, 157.33, 145.01, 142.49, 141.90, 130.29, 129.38, 129.31, 121.55, 121.22, 118.48, 114.43, 111.87,

111.42, 111.17, 110.41, 107.16, 95.56, 55.66, 55.14, 49.87, 41.13, 36.07. ESI-MS: mass calcd for $[M + H]^+$ ($C_{30}H_{32}N_2O_4$) 485.24; found m/z, 484.25. Purity 98.1% by HPLC.

3-(3,5-dimethoxy-4-(((3-(4-methoxyphenyl)propyl)amino)methyl)phenoxy)-N-phenylaniline (35). The title compound was prepared from **6a** and 3-(4-methoxyphenyl)propan-1-amine following the general procedure of **B**. Yield: 55.61 %, brown oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 – 7.22 (m, 2H), 7.18 (t, *J* = 8.1 Hz, 1H), 7.11 – 7.05 (m, 4H), 6.93 (t, *J* = 7.3 Hz, 1H), 6.83 – 6.77 (m, 3H), 6.70 (t, *J* = 2.2 Hz, 1H), 6.56 – 6.51 (m, 1H), 6.24 (s, 2H), 5.87 (s, 1H), 3.83 (s, 2H), 3.76 (s, 3H), 3.73 (s, 6H), 2.60 (dt, *J* = 24.7, 7.5 Hz, 4H), 1.88 – 1.77 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.47, 158.32, 157.72, 157.59, 145.03, 142.49, 134.26, 130.31, 129.38, 129.29, 121.56, 118.50, 113.75, 111.94, 110.60, 110.49, 107.26, 95.52, 55.77, 55.27, 48.19, 40.99, 32.66, 31.33. ESI-MS: mass calcd for $[M + H]^+$ ($C_{31}H_{34}N_2O_4$) 499.25; found m/z, 499.26. Purity 98.6% by HPLC.

3-(3-methoxy-4-(((4-methoxyphenethyl)amino)methyl)phenoxy)-N-phenylaniline (36). The title compound was prepared from **6b** and 2-(4-methoxyphenyl)ethan-1-amine following the general procedure of **B**. Yield: 50.09 %, brown solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (dd, *J* = 11.2, 4.6 Hz, 2H), 7.16 (t, *J* = 8.1 Hz, 1H), 7.12 (d, *J* = 8.1 Hz, 1H), 7.10 – 7.04 (m, 4H), 6.92 (t, *J* = 7.3 Hz, 1H), 6.84 – 6.79 (m, 2H), 6.79 – 6.75 (m, 1H), 6.69 (t, *J* = 2.2 Hz, 1H), 6.56 (d, *J* = 2.2 Hz, 1H), 6.51 (ddd, *J* = 7.6, 5.6, 2.0 Hz, 2H), 5.83 (s, 1H), 3.76 (s, 5H), 3.67 (s, 3H), 2.84 (dd, *J* = 10.9, 4.2 Hz, 2H), 2.77 (dd, *J* = 10.7, 3.9 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.71, 158.44, 158.06, 157.29, 144.99, 142.49, 131.96, 130.64, 130.31, 129.69, 129.38, 122.74, 121.54, 118.50, 113.90, 111.96, 110.61, 110.32, 107.37, 102.46, 55.34, 55.29, 50.33, 48.72, 35.08. ESI-MS: mass calcd for $[M + H]^+$ ($C_{29}H_{30}N_2O_3$) 455.23; found m/z, 455.23. Purity 95.4% by HPLC.

3-(2-methoxy-4-(((4-methoxyphenethyl)amino)methyl)phenoxy)-N-phenylaniline (37). The title compound was prepared from **6c** and 2-(4-methoxyphenyl)ethan-1-amine following the general procedure of **B**. Yield: 55.62 %, brown oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 – 7.20 (m, 2H), 7.12 (t, *J* = 8.2 Hz, 3H), 7.06 – 7.02 (m, 2H), 6.96 – 6.88 (m, 3H), 6.85 – 6.78 (m, 3H), 6.71 (dd, *J* = 8.0, 1.5 Hz, 1H), 6.64 (t, *J* = 2.2 Hz, 1H), 6.45 (dd, *J* = 7.9, 2.0 Hz, 1H), 5.76 (s, 1H), 3.80 (s, 3H), 3.76 (s, 5H), 2.88 (t, *J* = 6.8 Hz, 2H), 2.78 (t, *J* = 6.9 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.21, 158.13, 151.46, 144.70, 143.78, 142.69, 136.86, 131.86, 130.09, 129.68, 129.32, 121.28, 121.08, 120.63, 118.30, 113.98, 112.67, 111.45, 109.28, 106.14, 56.02, 55.29, 53.54, 50.62, 35.21. ESI-MS: mass calcd for $[M + H]^+$ ($C_{29}H_{30}N_2O_3$) 455.23; found m/z, 455.24. Purity 97.3% by HPLC.

3-(4-(((4-methoxyphenethyl)amino)methyl)phenoxy)-N-phenylaniline (38). The title compound was prepared from **6d** and 2-(4-methoxyphenyl)ethan-1-amine following the general procedure of **B**. Yield: 53.78 %, brown oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 – 7.19 (m, 4H), 7.14 (t, *J* = 8.1 Hz, 1H), 7.09 (d, *J* = 8.6 Hz, 2H), 7.03 (dd, *J* = 8.5, 1.0 Hz, 2H), 6.98 – 6.93 (m, 2H), 6.90 (dd, *J* = 10.5, 4.2 Hz, 1H), 6.84 – 6.79 (m, 2H), 6.76 – 6.72 (m, 1H), 6.67 (t, *J* = 2.2 Hz, 1H), 6.51 – 6.47 (m, 1H), 5.79 (s, 1H), 3.74 (s, 3H), 3.73 (s, 2H), 2.85 (dd, *J* = 10.8, 3.8 Hz, 2H), 2.74 (t, *J* = 7.0 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.64, 158.12, 156.01, 145.01, 142.56, 135.30, 132.06, 130.35, 129.71, 129.54, 129.42, 121.53, 119.11, 118.52, 114.01, 111.96, 110.70, 107.49, 55.31, 53.32, 50.76, 35.41. ESI-MS: mass calcd for $[M + H]^+$ ($C_{28}H_{28}N_2O_2$) 425.22; found m/z, 425.23. Purity 98.2% by HPLC.

Synthesis of 4-(phenylamino)phenol (40). The title compound was prepared from 4-aminophenol and bromobenzene following procedure the same as compound **5**. Yield: 82.37 %, brown solid. ^{1}H

NMR (400 MHz, $CDCl_3$) δ 7.24 – 7.18 (m, 2H), 7.04 – 6.99 (m, 2H), 6.93 – 6.86 (m, 2H), 6.83 (t, *J* = 7.3 Hz, 1H), 6.80 – 6.74 (m, 2H), 5.46 (s, 1H), 4.64 (s, 1H). ESI-MS: mass calcd for $[M + H]^+$ ($C_{12}H_{11}NO$) 186.08; found m/z, 186.09.

Synthesis of 2,6-dimethoxy-4-(4-(phenylamino)phenoxy)benzaldehyde (41). The title compound was prepared from 40 and 4-fluoro-2,6-dimethoxybenzaldehyde following general procedure A. Yeid:76.55%, colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 10.32 (s, 1H), 7.26 – 7.21 (m, 2H), 7.07 – 7.02 (m, 4H), 6.96 (d, *J* = 8.8 Hz, 2H), 6.93 (t, *J* = 7.4 Hz, 1H), 6.12 (s, 2H), 3.72 (s, 6H). ESI-MS: mass calcd for $[M + H]^+$ ($C_{21}H_{19}NO_4$) 350.13; found m/z, 350.14.

4-(3,5-dimethoxy-4-(((4-methoxyphenethyl)amino)methyl)phenoxy)-N-phenylaniline (42). The title compound was prepared from **41** and 2-(4-methoxyphenyl)ethan-1-amine following the general procedure of **B.** Yield: 56.35 %, brown oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.25 (t, *J* = 7.8 Hz, 2H), 7.08 (t, *J* = 8.3 Hz, 4H), 7.01 (d, *J* = 8.1 Hz, 2H), 6.95 (d, *J* = 8.8 Hz, 2H), 6.90 (t, *J* = 7.3 Hz, 1H), 6.81 (d, *J* = 8.5 Hz, 2H), 6.17 (s, 2H), 5.68 (s, 1H), 3.84 (s, 2H), 3.77 (s, 3H), 3.66 (s, 6H), 2.81 (dd, *J* = 13.1, 5.6 Hz, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.38, 158.75, 157.99, 150.95, 143.82, 138.93, 132.05, 129.69, 129.40, 120.63, 120.28, 120.09, 116.99, 113.82, 109.89, 94.39, 55.66, 55.28, 49.97, 41.03, 34.86. ESI-MS: mass calcd for $[M + H]^+$ ($C_{30}H_{32}N_2O_4$) 485.24; found m/z, 485.25. Purity 98.6% by HPLC.

4-(3,5-dimethoxy-4-(((3-methoxyphenethyl)amino)methyl)phenoxy)-N-phenylaniline(43). The title compound was prepared from **41** and 2-(3-methoxyphenyl)ethan-1-amine following the general procedure of **B.** Yield: 51.21 %, brown oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.28 – 7.25 (m, 1H), 7.24 (dd, *J* = 5.7, 3.8 Hz, 1H), 7.21 – 7.16 (m, 1H), 7.09 – 7.05 (m, 2H), 7.01 (dd, *J* = 8.6, 1.0 Hz, 2H), 6.98 – 6.93 (m, 2H), 6.90 (t, *J* = 7.3 Hz, 1H), 6.79 – 6.71 (m, 3H), 6.17 (s, 2H), 5.66 (s, 1H), 3.85 (s, 2H), 3.77 (s, 3H), 3.65 (d, *J* = 7.9 Hz, 6H), 2.85 (dd, *J* = 12.5, 5.6 Hz, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.02, 159.93, 159.71, 149.71, 143.49, 139.68, 138.95, 129.77, 129.42, 121.13, 120.95, 120.90, 119.69, 117.32, 114.23, 112.53, 93.70, 55.82, 55.22, 47.29, 40.00, 32.87. ESI-MS: mass calcd for $[M + H]^+$ ($C_{30}H_{32}N_2O_4$) 485.24; found m/z, 485.25. Purity 95.8% by HPLC.

4-(3,5-dimethoxy-4-(((2-methoxyphenethyl)amino)methyl)phenoxy)-N-phenylaniline(44). The title compound was prepared from **41** and 2-(2-methoxyphenyl)ethan-1-amine following the general procedure of **B.** Yield: 47.38 %, brown oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.19 (d, *J* = 7.2 Hz, 1H), 7.16 (s, 1H), 7.12 – 7.05 (m, 2H), 7.02 – 6.98 (m, 2H), 6.94 (dd, *J* = 8.5, 0.9 Hz, 2H), 6.90 – 6.85 (m, 2H), 6.84 (d, *J* = 7.3 Hz, 1H), 6.80 – 6.77 (m, 1H), 6.75 (d, *J* = 8.2 Hz, 1H), 6.10 (s, 2H), 5.60 (s, 1H), 3.79 (s, 2H), 3.70 (s, 3H), 3.59 (s, 6H), 2.79 (s, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.92, 159.60, 157.50, 149.69, 143.45, 139.75, 131.18, 129.42, 128.49, 125.30, 120.93, 120.86, 120.83, 119.65, 117.36, 110.48, 93.75, 55.82, 55.20, 45.68, 40.21, 28.44. ESI-MS: mass calcd for $[M + H]^+$ ($C_{30}H_{32}N_2O_4$) 485.24; found m/z, 485.25. Purity 96.1% by HPLC.

4-(3,5-dimethoxy-4-(((3-(4-methoxyphenyl)propyl)amino)methyl)phenoxy)-N-phenylaniline(45). The title compound was prepared from **41** and 3-(4-methoxyphenyl)propan-1-amine following the general procedure of **B.** Yield: 53.13 %, brown oil.^1H NMR (400 MHz, $CDCl_3$) δ 7.28 (s, 1H), 7.24 (s, 1H), 7.10 – 7.06 (m, 3H), 7.05 – 7.01 (m, 3H), 6.98 – 6.94 (m, 2H), 6.90 (dd, *J* = 11.6, 4.1 Hz, 1H), 6.81 – 6.77 (m, 2H), 6.18 (s, 2H), 5.69 (s, 1H), 3.94 (s, 2H), 3.76 (s, 3H), 3.73 (s, 6H), 2.71 – 2.66 (m, 2H), 2.59 – 2.54 (m, 2H), 1.97 – 1.90 (m, 2H). ^{13}C NMR (101 MHz, CDCl3) δ 160.89, 159.85, 157.92, 149.86, 143.53, 139.59, 132.78, 129.42, 129.29, 120.90, 120.87, 119.76, 117.28, 113.83, 93.71, 55.85, 55.24, 45.80, 39.55, 32.16, 28.18. ESI-MS: mass calcd for $[M + H]^+$

($C_{31}H_{34}N_2O_4$) 499.25; found m/z, 499.26. Purity 95.8% by HPLC.

4.2. Biological Assays

4.2.1 ***Cell culture.*** All the cell licenced in this investigation were obtained from the American Type Culture Collection (Manassas, VA, USA). Cells were cultured at 37 ^oC with 5% CO_2 in RPMI 1640, L-15 Medium or DMEM, supplemented with 10%(v/v) fetal bovine serum (Gibco) and 1%(v/v) penicillin-streptomycin (HyClone).

4.2.2 ***Cell viability assay.*** Evaluation of cytotoxicity was performed using the MTT assay. Cells were seeded at a cell density of 2-4 $x10^3$ cells/0.1 mL/well in a 96-well plate. The compounds were added 24 h plating at the indicated concentrations. After treatment for 72 h, a volume of 20 μL of MTT solution (5 mg/mL) was added to each well and incubated for additional 2-4 h incubation at 37 ^oC. Then the medium was discarded, and the formazan salt was dissolved with 150 μL DMSO for10-15 min. The absorbance values (OD) of the 96-well plate was measured at 570 nm using a Spectra MAX M5 microplate spectrophotometer (Molecular Devices, CA, USA). The IC_{50} values were the means of at least three independent experiments and calculated by GraphPad Prism5 software.

4.2.3 ***Purification of c-Myc and Max.*** Human Myc bHLHZip domain (residues 353-439), and Max(S) (151 amino acids residues) were expressed in *Escherichia coli* strain BL21DE3 an N-terminal hexa-histidine (His 6) tag proteins by backbone vector pET151D/-TOPO. Bacterial culture and protein purification were conducted by previous published methods[61, 62], Bacteria were cultured at 37 ^oC, 225 rpm for overnight and for another 20 h to express proteins in 0.8 mM isopropyl-L-thio-B-D-galactopyranoside (IPTG, Sigma). Then, cultures were harvested and lysed in a buffer (8 M urea, 100 mM NaH_2PO_4, and 10 mM Tris), proteins were purified by NTA-Ni-agarose chromatography columns (Qiagen, Inc. Chatsworth) and dialyzed in storage buffer(TrisHCl 50 mM, pH 6.5, NaCl 150 mM, and 30% glycerol). Proteins were quantified by using Nanodrop and utilized in Enzyme-Linked Immunosorbent Assay (ELISA) and Electrophoretic Mobility-Shift Assay (EMSA).

4.2.4 ***Enzyme-Linked Immunosorbent Assay.*** Purified Myc bHLHZip domain (5.5 μg, 50 μL/well, in 1 x buffer: 10mM EDTA, 1 × PBS (pH = 7.0), 500 mM KCl, 30 mM $MgCl_2$, 5% glycerol, 0.1% NP40, 1.5mM DTT) were coated on an ELISA plate (Costar) at 4 ^oC for 24 h. The plates were rinsed with 1 x buffer for three times and blocked with 200 μL (per well) of blocking buffer (3% BSA, 0.5 x buffer) for 2 h at 37 ^oC. Then rinsing three times with 1 x buffer for a total 40min, 100 μL of 1 x buffer containing Max (6.5 μg/per well) and different concentrations of compounds (10 μM, 30 μM, 60 μM, 90 μM, 120 μM, 150 μM.) were added to the wells, DMSO as vehicle control, c-Myc/MAX inhibitor sAJM589 as positive control. All test mixtures contained 5% DMSO. The plates were incubated for 1 h at 37°C and 30 min at 23°C, wells were washed four times with 0.5 x buffer and incubated with rabbit anti-c-Myc antibody (ab39688, Abcam) for 1 h at 37°C. Then washed three times with 1 x buffer, 100 μL of the same buffer containing a secondary HRP goat anti-rabbit IgG (ab205718, Abcam) was added and incubated for 1.5 hour at 37°C, tetramethylbenzidine (TMB, Sigma)was added to measure enzyme activity, and the absorption at 450 nm was detected by Spectra MAX M5 microplate spectrophotometer (Molecular Devices, CA, USA). Data was analyzed by GraphPad Prism5 software.

4.2.5 ***Electrophoretic Mobility-Shift Assay.*** EMSA were prepared as previously reported methods[24, 56], the double-stranded DNA biotinylated oligonucleotide (5-CACCCGGTCACGTGGCCTACAC-3, 50 nM) containing c-Myc/Max dimers binding site and purified proteins (Myc/Max complex, 50 nM) were performed. Binding reaction buffer contained 10mM EDTA, 1 × PBS (pH = 7.0), 500 mM KCl, 30 mM $MgCl_2$, 5% glycerol, 0.1% NP40, 1.5mM DTT, 10%DMSO. Compounds were dissolved in DMSO for test, DMSO as control. Proteins interaction complex and 20 μM compounds were prepared for 1.5 h at room temperature, then added the DNA oligo for further 0.5 h. Data were detected by BioRad FX molecular imager (BioRad, CA) and analyzed by Image J (Bio-Rad, USA).

4.2.6 ***Molecular docking study.*** To apprehend the potential binding modes of **42** in c-Myc/Max, molecular docking analysis was performed using Discovery Studio 3.5(DS 3.5, Accelrys Inc., San Diego, CA, USA). The crystal structure of the Myc-Max (PDB ID:1NKP) was obtained from the RCSB Protein Data Bank. The crystal structure of the c-Myc/Max domain were removed water molecules and hydrogen atoms were added to the protein. In the course of docking, the binding site was set 15 Å, and the other docking parameters were set as default value.

4.2.7 ***Flow cytometry***. Flow cytometry (FCM) was used to detect the cell cycle distribution and the cell apoptosis rate induced by compound **42**. HT29 cells and HCT15 cells were seeded in a 6-well plate at 3×10^5 cells per well and incubated for 24 h, and treated with compound **42** for 24 h respectively. Cells were harvested and fixed with ice-cold 70% ethanol at 4 ºC for 12 h, and then ethanol was removed and the cells were washed with cold PBS. After that, the cells were detached from the plate using trypsinization, collected by centrifugation at 1000 rpm for 5min. Then the cells were resuspended in binding buffer and stained by Cell Cycle Detection Kit (keygentec, KGA512) and Annexin V-FITC/PI double-labeling (keygentec, KGA107). The resulting samples were analyzed by flow cytometry using an ACEA NovoCyte Advanteon (ACEA Biosciences Inc, USA).

4.2.8 ***Western blot analysis.*** Cells were seeded in 60 × 15 mm dishes overnight prior to treatment and incubated with the indicated doses of compound **42** for 24 h at 37 °C.Then, cell pellets were collected and resuspended withNP40 lysis buffer (Beyotime), which was added with extra-proteasome inhibitor PMSF and phosphatase inhibitor Cocktail(Sigma). Whole-cell protein lysates were incubated on ice for 30 min and centrifuged at 12000 rpm and 4 °C for 20 min. The supernatants were determined using the BCA ProteinAssay Kit (Solarbio PC0020). The samples were separated by SDS-PAGE (sodium dodecyl sulfate-polyacrylamide gel electrophoresis) and transferred to polyvinylidene fluoride membranes (Millipore). The membranes were incubated at 4 °C overnight with the primary antibodies in 5% BSA/TBST buffer with gentle shaking. After washing, the membranes were incubated for 1 h at room temperature with appropriate peroxidase-conjugated secondary antibodies (anti-IgG-HRP1:5000, CST) and washed again, protein bands were visualized using enhanced ECL western blotting detection reagents (Millipore) followed by capturing photos with chemiluminescence system. Antibody information: c-Myc Antibody (1/1000dilution, CST#9402), β-actin (1/1000dilution, CST#4970).

4.2.9 ***Colony formation assay.*** To test the survival of cells treated with compound **42**, HT29 cells and HCT15 cells (500 cells/well) were plated in a 6-well plate and incubated overnight at 37 °C, followed by the indicated doses of compound **42** (0 - 5.0 μM, DMSO as control) for 15 days with fresh medium. The cell culture was terminated when the cell formed colony was observed, then the supernatant was

removed and washed with PBS buffer solution for two times, then it was fixed with 4% polyformaldehyde for 15 min, before the solution was abandoned. Colonies were fixed with 4% paraformaldehyde and stained with a 0.5% crystal violet solution for 15 min, then the crystal violet solution was removed and PBS buffer solution was used to scour off the dyeing liquor. The data were expressed from three independent experiments. The number of colonies in treated cultures was expressed as a percentage of the control cultures.

4.2.10 ***In Vivo Study.*** Animal studies were conducted under the approval of the Experimental Animal Management Committee of Sichuan University. The female BALB/c nude mice were purchased (Beijing HFK Bioscience Co. ltd., Beijing, China). HT29 cells (8×10^6) were injected subcutaneously into 6−7 weeks old female BALB/c mice. Once the average tumor volume grew to approximately 100 mm^3, the mice were divided into five groups randomly (n=5, each group). The mice were treated daily for 30 days by via oral gavage administration with vehicle control(10%DMSO, 1%Tween-80 and saline), **42**(40mg/kg, 80mg/kg, 120mg/kg dissolved in 10%DMSO, 1%Tween-80 and saline), 5-Fluorouracil (positive control, 30mg/kg dissolved in 10%DMSO, 1%Tween-80 and saline) .Tumor size and body weights were determined every two days. The tumor volume was measured by Vernier calipers and calculated as [0.5 x shortest diameter^2 x longest diameter]. Inhibition rate of tumor growth was calculated using the following formula: 100 × {1 − [(tumor volume final − tumor volume initial) for treated group]/ [(tumor volume final − tumor volume initial) for the vehicle-treated group]}.

4.3 ***Statistical analysis.*** Data were analyzed by using descriptive statistics, single factor analysis of variance (ANOVA), and presented as mean values ± standard deviation (SD). Statistical analysis of all results (mean ± SEM) was evaluated by unpaired t test: *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$, NS (no significance): $p > 0.05$.

NOTES

The authors declare no competing interest.

ACKNOWLEDGMENTS

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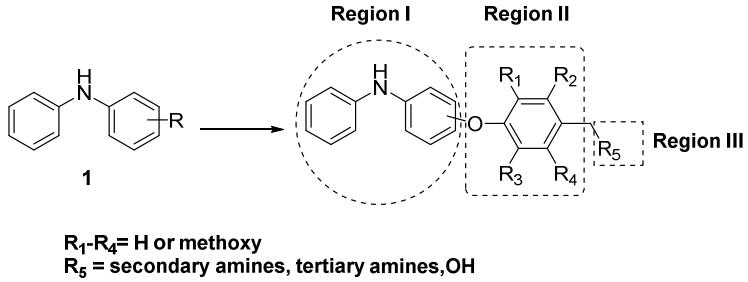
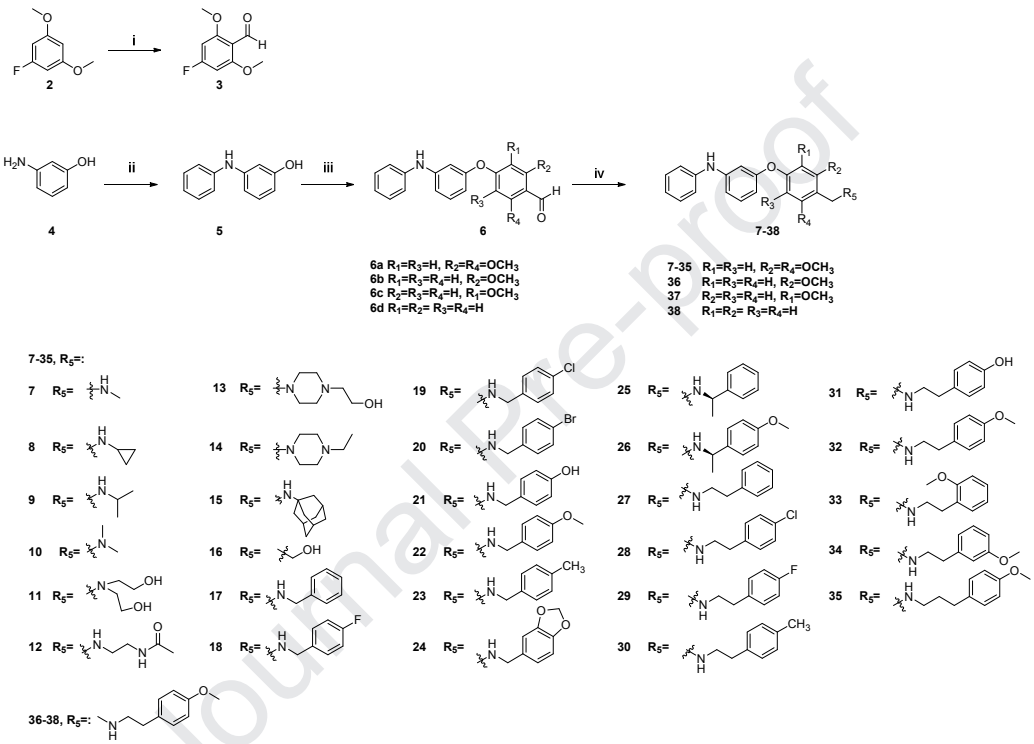
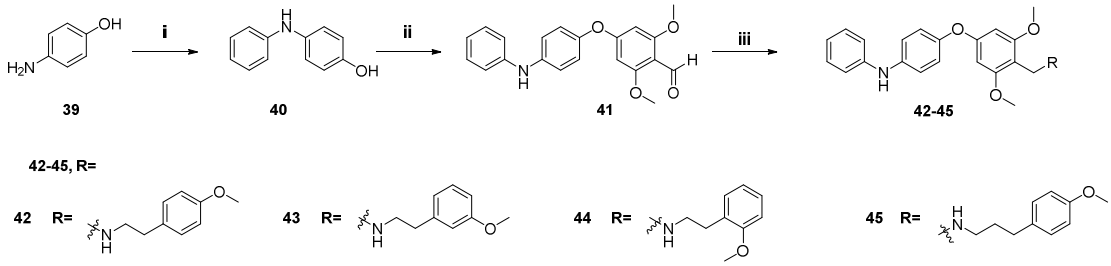


Scheme 1. Design of series derivatives based on c-Myc inhibitors.



Scheme 2. **Synthetic Routes for Compounds 7-38**

Reagents and conditions: (□) $POCl_3$, DMF, 0 °C to 60 °C, 4 h. 62%; (□) bromobenzene, t-BuONa, BrettPhos Palladacycle, 1,4-dioxane, 90°C, 2h. 86%; (□) substituted 4-fluorobenzaldehydehyde, K_2CO_3, DMSO, 100 °C, 3 h. 73%-85%; (□) Amine, $NaBH(AcO)_3$, AcOH, DMF, 80 °C, overnight. 45%-60%.



Scheme 3. **Synthetic Routes for Compounds 42-45**

Reagents and conditions: (□) bromobenzene, t-BuONa, BrettPhos Palladacycle, 1,4-dioxane, 90°C, 2h. 82%; (□) 1-Fluoro-3,5-dimethoxybnzene, K_2CO_3, DMSO, 100 °C, 3 h. 76%; (□) Amine, $NaBH(AcO)_3$, AcOH, DMF, 80 °C, overnight. 47%-56%.

Table 1. In *vitro* antiproliferative activities

Compound	$IC_{50}(\mu M)$ [a]				
	Cell lines				
	HT29	HCT15	HCT116	DLD-1	SW620
7	7.43±0.81	8.93±0.62	>20	11.87±1.23	15.04±1.52
8	12.28±1.17	6.14±0.56	>20	>20	>20
9	>20	>20	>20	>20	>20
10	>20	15.61±1.02	12.86±0.95	>20	>20
11	>20	8.97±0.49	>20	>20	>20
12	3.96±0.17	5.09±0.33	18.2±1.82	6.01±0.32	11.93±1.07
13	>20	6.43±0.57	>20	>20	>20
14	>20	5.09±0.43	>20	>20	>20
15	3.53±0.07	6.51±0.18	>20	7.37±0.67	>20
16	13.88±2.01	12.13±1.36	>20	18.13±2.21	>20
17	3.34±0.67	5.02±0.23	4.07±0.82	5.22±0.16	7.49±0.54
18	2.75±0.33	3.64±0.25	4.22±0.38	2.65±0.72	6.77±0.47
19	3.35±0.14	4.85±0.29	3.31±0.36	3.74±0.42	6.34±0.87
20	3.06±0.38	5.41±0.46	6.23±0.31	3.52±0.50	11.21±0.11
21	2.18±0.12	3.43±0.28	3.36±0.39	2.69±0.15	7.94±0.92
22	1.89±0.14	2.65±0.12	2.62±0.55	1.91±0.23	6.97±0.46
23	3.88±0.18	5.40±0.39	13.81±1.95	6.08±0.82	11.79±2.28
24	8.50±0.62	8.93±0.83	>20	8.57±1.36	>20
25	5.12±0.58	7.55±0.77	>20	8.57±0.95	18.67±1.82
26	1.63±0.04	4.69±0.24	2.44±0.18	3.50±0.56	8.25±0.37
27	6.06±0.47	6.14±0.30	13.63±0.93	6.77±0.49	11.62±1.39
28	2.82±0.28	3.76±0.12	5.40±0.39	3.40±0.13	10.04±0.72
29	2.52±0.18	2.34±0.09	3.19±0.13	2.87±0.35	8.95±0.14
30	1.25±0.06	2.88±0.16	3.32±0.22	1.86±0.09	5.77±0.41
31	2.93±0.08	6.14±0.39	15.73±2.15	4.03±0.26	12.70±1.82
32	1.02±0.21	1.25±0.13	0.98±0.12	1.12±0.05	6.23±0.43
33	2.12±0.38	1.19±0.34	3.40±0.18	2.32±0.29	3.65±0.12
34	2.33±0.31	1.29±0.06	4.02±0.24	2.35±0.12	3.93±0.09
35	3.32±0.21	0.73±0.18	2.85±0.13	2.54±0.06	6.40±0.68
36	3.97±0.08	1.02±0.05	2.67±0.51	4.06±0.28	7.84±0.06
37	2.75±0.25	3.35±0.51	3.11±0.04	5.92±0.19	10.96±1.33
38	6.89±0.14	2.18±0.12	3.99±0.27	4.65±0.06	14.60±1.85
42	0.32±0.05	0.51±0.09	0.82±0.32	1.31±0.26	3.78±0.54
43	3.62±0.14	1.65±0.17	3.91±0.26	5.47±0.08	6.12±0.31
44	2.21±0.19	3.77±0.24	4.1±0.16	3.59±0.27	8.76±0.51
45	6.89±0.36	2.18±0.13	3.23±0.08	4.65±0.22	14.60±2.11
Cisplatin	10.75±0.97	8.92±0.32	13.78±1.21	15.22±2.16	17.35±1.62
5-Fluorouracil	13.37±1.08	10.86±0.91	12.31±1.51	11.40±1.32	15.29±1.48

[a]IC50, the mean ± SD value of triplicate measurement, inhibitory activity was assayed by treatment with

substances for 72 h.

Table 2. The compounds binding inhibition of Myc/Max dimerization confirmed by ELISA

Compound	ELISA IC_{50}(μM) [a]	Compound	ELISA IC_{50}(μM)
7	>150	**26**	108±25
8	>150	**27**	96±18
9	>150	**28**	92±20
10	>150	**29**	95±25
11	>150	**30**	87±12
12	>150	**31**	83±14
13	>150	**32**	69±15
14	>150	**33**	72±19
15	147±21	**34**	78±16
16	>150	**35**	147±21
17	125±15	**36**	102±17
18	137±20	**37**	107±14
19	123±18	**38**	116±15
20	129±17	**42**	63±13
21	123±16	**43**	75±16
22	86±15	**44**	147±21
23	119±20	**45**	72±15
24	105±18	**sAJM589**	36±9
25	116±22		

[a]IC50, the mean ± SD value of triplicate measurement.

Table 3. The compounds binding inhibition rates at 20 μM detected by EMSA

Compound	Relative inhibition (%) [a]	Compound	Relative inhibition (%)
7	2.5	**26**	36.1
8	1.7	**27**	45.1
9	N/A[b]	**28**	43.7
10	3.2	**29**	40.5
11	6.1	**30**	46.2
12	10.2	**31**	51.7
13	N/A	**32**	75.1
14	8.9	**33**	67.4
15	12.6	**34**	60.8
16	N/A	**35**	63.4
17	26.4	**36**	42.1
18	21.2	**37**	42.3
19	25.7	**38**	35.6
20	29.3	**42**	83.2
21	31.8	**43**	65.2
22	48.7	**44**	57.3
23	32.4	**45**	70.6
24	42.1	**DMSO**	0
25	30.5		

[a] Relative inhibition was calculated by the ratio of experimental group and control (DMSO)

[b] Not tested

All data represent three independent experiments.

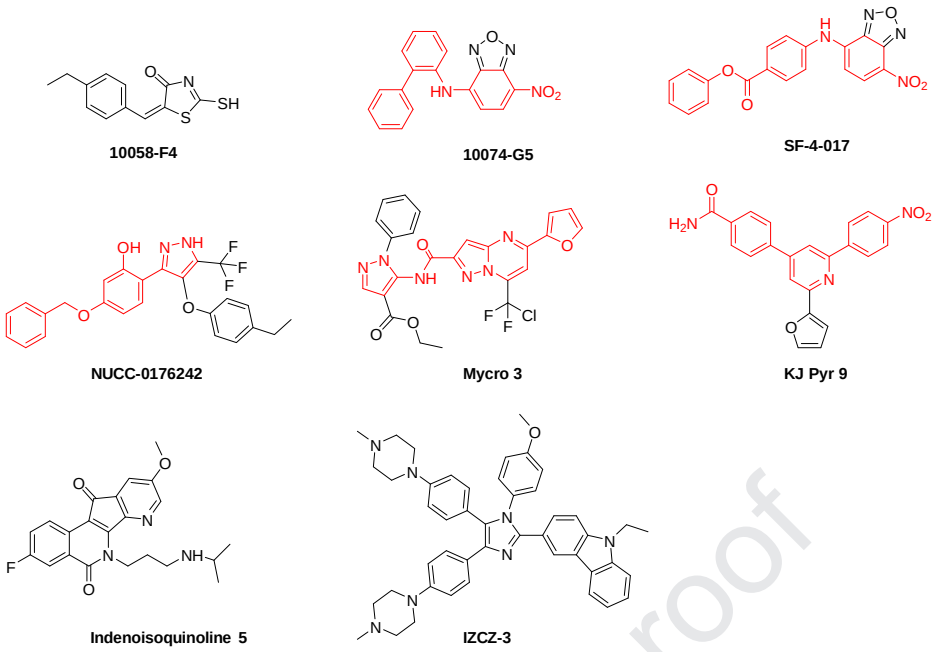


Figure 1. Chemical structures of previously reported c-Myc inhibitors.

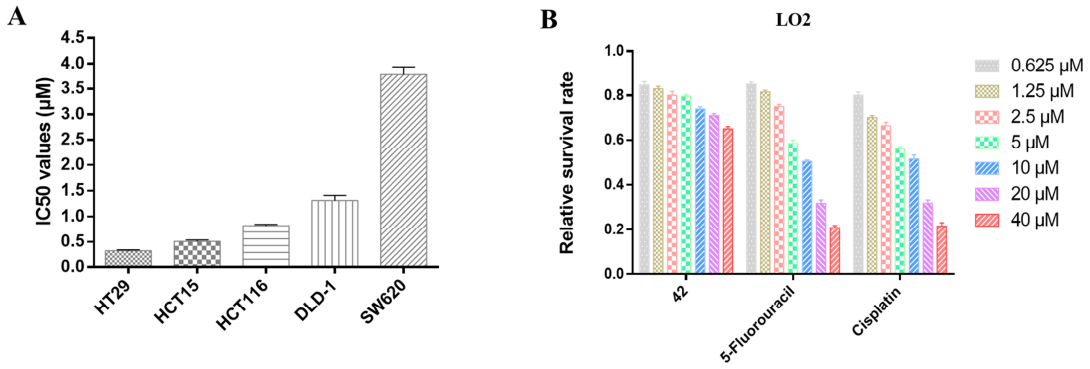


Figure 2. The effect of compound **42** on CRC cells and normal liver cell LO2 viability. (A) The compound **42** with IC50 in HT29, HCT15, HCT116, DLD-1, respectively. (B) Toxicities of **42**, 5-Fluorouracil, and Cisplatin against LO2. The data were expressed from three independent experiments (N = 3 per group, mean ± SD).

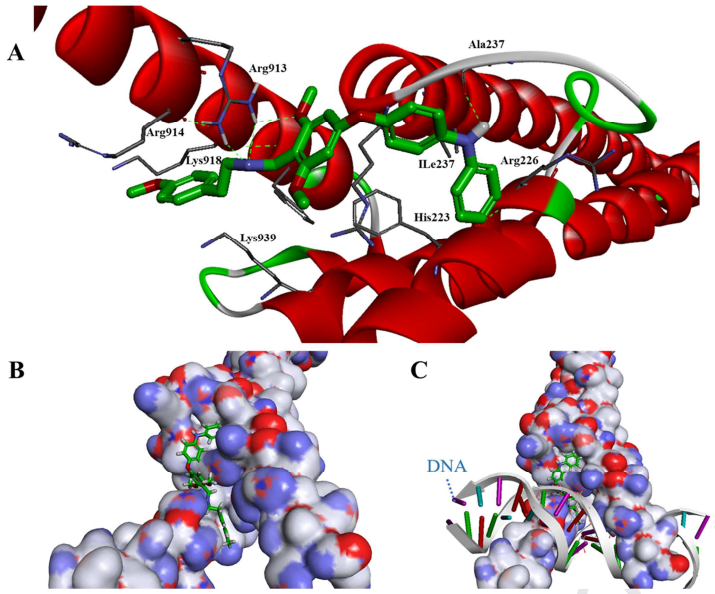


Figure 3. (A) Predicted binding modes of **42**(green) with key amino acid residues of c-Myc/Max. (B) Predicted binding modes of **42** in c-Myc/Max dimer face. (C) In silico binding mode of **42** complex with Myc-Max-DNA. (PDB code: 1NKP).

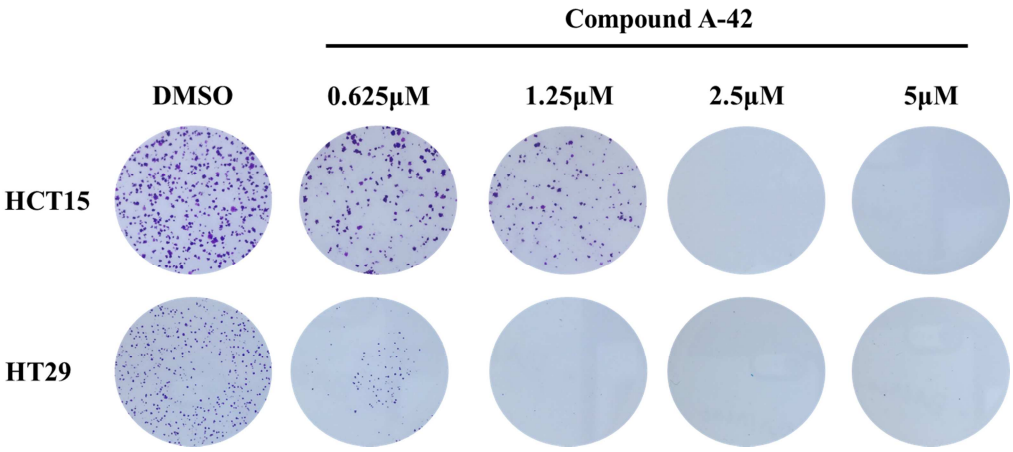


Figure 4. Colony formation assay of **42** in HT29, HCT15. The colony clusters were detected after 15days treatment with **42**.

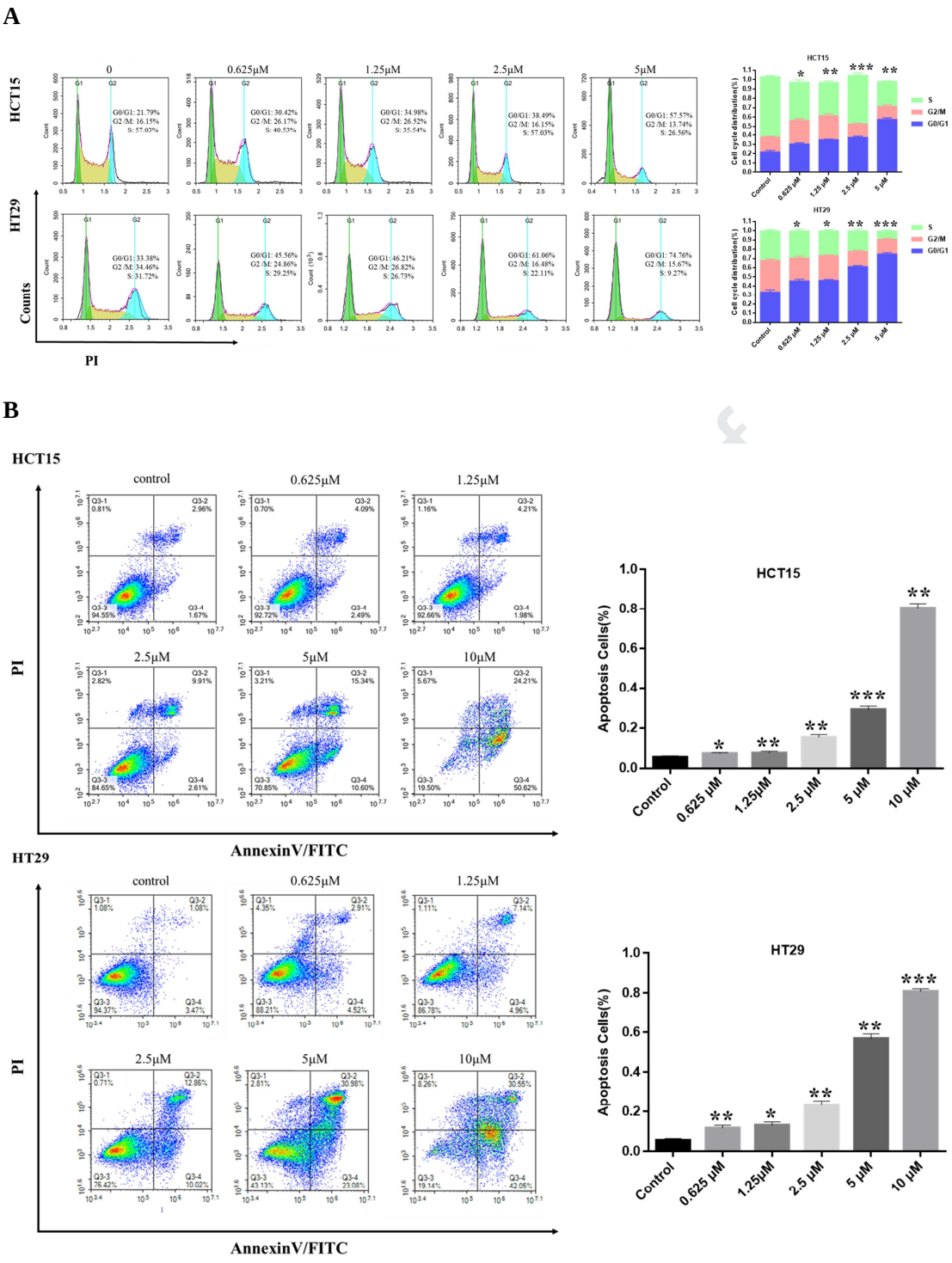


Figure 5. Flow cytometry of compound **42**. (A) Cells were cultured with **42** from 0 to 5 μM for 24 h, the cell cycle distribution was analyzed by flow cytometry after propidium iodide staining. (B) Cells were treated with indicated concentrations of compound **42** for 24 h, and the level of apoptosis was evaluated by FITC-Annexin V/PI and analysis of apoptotic cells analyzed by flow cytometry. Data shown were from three independent experiments (N = 3 per group, mean ± SD). *P < 0.05 vs DMSO, **P < 0.01 vs DMSO; ***P < 0.001 vs DMSO.

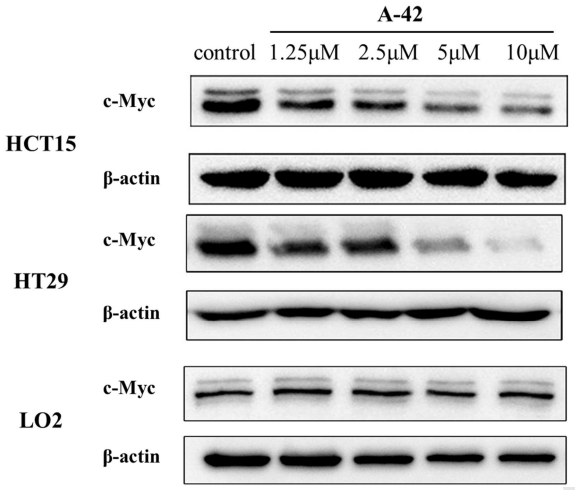


Figure 6. Effects of **42** on c-Myc expression was determined by Western blotting. Cells were treated with indicated dose of **42** for 24h. All of the experiments were repeated three independent times

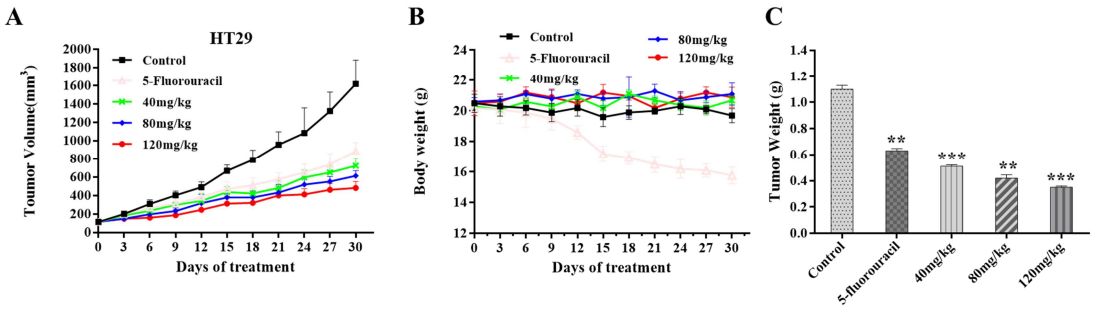


Figure 7. In *vivo* efficacy of **42** in HT29 tumor xenograft model (N = 5 per group, mean ± SD). (A) Growth inhibitory effect of **42** treated on HT29 xenograft tumor in female BALB/c nude mice. (B) Average body weights of the mice in each group during 30days treatment. (C) Tumor weights of the mice in each group when the treatment ended. **P < 0.01 vs DMSO; ***P < 0.001 vs DMSO.

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RESEACH HILIGHTS

- Novel 3(or4)-(phenoxy)-N-phenylaniline derivatives were designed and synthesized.
- In *vitro* study manifested that **42** showed remarkable activity with lower toxicity, could also induce cell apoptosis and arrest cell cycle distribution at G0/G1 phase.
- Compound **42** exhibited a good binding affinity to c-Myc/Max dimerization and DNA complex.
- Compound **42** displayed downregulation the c-Myc expression level by western blot.
- Compound **42** showed potent effect in *vivo* with low toxicity.

Declaration of Interest statement：

The authors declared that they have no conflicts of interest to this work. We declare that we do not have any commercial or associative interest that represents a conflict of interest in connection with the work submitted.