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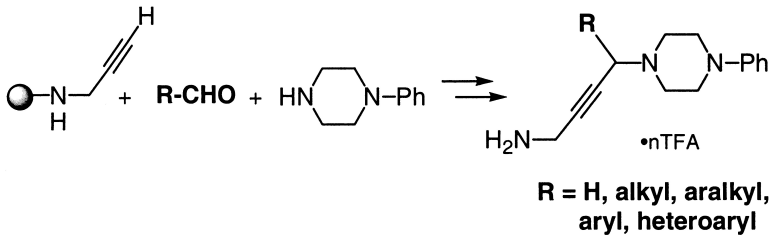


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# Solid-Phase Mannich Condensation of Amines, Aldehydes, and Alkynes: Investigation of Diverse Aldehyde Inputs

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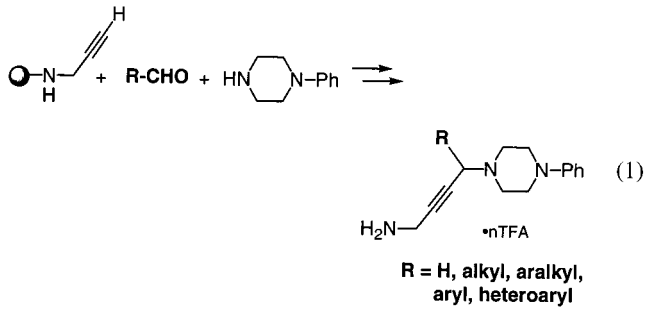
Terminal alkynes, secondary amines, and aldehydes undergo "solid-phase Mannich condensation". A set of diverse aldehyde inputs was examined. Aliphatic, aralkyl, aryl, and heteroaryl carboxaldehydes give good yields of Mannich adduct of high purity. Benzaldehydes containing electron-donating substituents that decrease the electrophilicity of the carbonyl center, or heteroaryl aldehydes that are similarly deactivated by resonance effects, do not undergo reaction.

The application of multicomponent reaction systems to solid-phase synthesis is a powerful strategy for the construction of structurally diverse compound libraries because several elements of diversity can be introduced in a single transformation.[1−5] In this context, the Mannich reaction[6,7] is particularly well-suited because the individual components, namely, an aldehyde, an amine, and an "active-hydrogen" compound such as a terminal alkyne, are ubiquitous simple organic units and because the resultant adducts can be further elaborated into well-recognized pharmacophores (e.g., α-substituted benzylamines). We recently reported on solid-phase Mannich reactions and demonstrated that any of the three components could be immobilized via attachment to a resin, thereby expanding the general utility of the methodology.[8−11] Herein we report the results of a study that probed the scope of this solid-phase Mannich methodology by investigating diverse aldehyde components in reaction with phenylpiperazine and a resin-immobilized terminal alkyne.

In our earlier report[8] a series of substituted piperidines and piperazines smoothly underwent Mannich condensation with a resin-bound terminal alkyne in the presence of paraformaldehyde. While this work demonstrated that a wide variety of functional groups and substituents, such as alcohol, ester, nitrile, amide, halo, nitro, and ether, are inert to solid-phase Mannich conditions, it was limited to cases involving an exceptionally reactive aldehyde, namely, paraformaldehyde. In fact, it should be noted that paraformaldehyde is typically the aldehyde component used in solution-phase Mannich condensations[6] involving terminal alkynes and that a systematic study of other aldehydes in the context of solid-phase Mannich methodology has yet to be reported.

With these issues in mind, a resin-bound terminal alkyne was treated with 4-phenylpiperazine and a series of aryl and heteroaryl aldehydes (eq 1) in the presence of copper(I) under uniform reaction conditions. Specifically, 1 mol equiv of propargylamine, immobilized on a chlorotrityl resin,[7] was reacted with 10 mol equiv of phenylpiperazine and 20 mol equiv of aldehyde in the presence of copper(I) chloride in dioxane at 75 °C for 4.5 h. After this time, the resin was filtered and successively washed to remove excess reagents and then air-dried. The products were cleaved from the resin by treatment with 25% trifluoroacetic acid/DCM and dried in vacuo. The crude products were each analyzed for purity by reverse-phase HPLC analysis, and the structure was confirmed by proton NMR and mass spectrometry.




(1)

Paraformaldehyde reacted efficiently as anticipated (**1**), and simple aliphatic aldehydes such as phenylacetaldehyde, diphenylacetaldehyde, cyclohexane carboxaldehyde, and even cinnamaldehyde similarly afforded Mannich adducts of high purity (**3**−**6**, respectively). Benzaldehyde smoothly underwent Mannich condensation (**2**) as did tolualdehydes (**15**−**17**) and naphthaldehydes (**24**−**25**). At this point, we decided to explore a series of substituted benzaldehydes in a systematic fashion. In particular, we were interested in exploring how aryl substituents that alter the reactivity of the aldehyde carbonyl center would influence the efficiency of the condensation. This feature is important in the context of selecting appropriate aldehyde inputs from the enormous number of commercially available aldehydes in order to prepare compound libraries.

Electron-deficient benzaldehydes proved to be exceptional substrates as evident by the series of chlorobenzaldehydes (**7**−**9**), dichlorobenzaldehyde (**10**), and trifluoromethylbenzaldehydes (**11**−**13**) regardless of the positioning of the electron-withdrawing substituent. Interestingly, the Mannich adduct of pentafluorobenzaldehyde (entry 14) was not isolated likely because of the instability of the final product

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**Table 1.** Mannich Reactions of Aldehydes and Phenylpiperazine with a Resin-Bound Alkyne[a]

| compd | R | HPLC purity, % | M + H$^+$ | compd | R | HPLC purity, % | M + H$^+$ |
|---|---|---|---|---|---|---|---|
| **1** | H | 83 | 230 | **14** | $C_6F_5$ | | no product |
| **2** | $C_6H_5$ | 95 | 306 | **15** | (2-Me)$C_6H_4$ | 95 | 320 |
| **3** | $CH_2-C_6H_5$ | 96 | 320 | **16** | (3-Me)$C_6H_4$ | 93 | 320 |
| **4** | $CHPh_2$ | 93 | 396 | **17** | (4-Me)$C_6H_4$ | 93 | 320 |
| **5** | cyclohexyl | 96 | 312 | **18** | (2-OMe)$C_6H_4$ | 93 | 336 |
| **6** | (*E*)-CH=CH-$C_6H_5$ | 66 | 332 | **19** | (3-OMe)$C_6H_4$ | 92 | 336 |
| **7** | (2-Cl)$C_6H_4$ | 91 | 340 | **20** | (4-OMe)$C_6H_4$ | | no product |
| **8** | (3-Cl)$C_6H_4$ | 92 | 340 | **21** | (3-OH)$C_6H_4$ | 92 | 322 |
| **9** | (4-Cl)$C_6H_4$ | 94 | 340 | **22** | (4-OH,3-OMe)$C_6H_3$ | | no product |
| **10** | (2,4-diCl)$C_6H_3$ | 90 | 374 | **23** | (4-Ph)$C_6H_4$ | 94 | 382 |
| **11** | (2-$CF_3$)$C_6H_4$ | 89 | 374 | **24** | 1-naphthyl | 91 | 356 |
| **12** | (3-$CF_3$)$C_6H_4$ | 87 | 374 | **25** | 2-naphthyl | 91 | 356 |
| **13** | (4-$CF_3$)$C_6H_4$ | 91 | 374 | | | | |
| | | | Heterocyclic | | | | |
| **26** | 2-pyridyl | | no product | **31** | 4-quinolinyl | | no product |
| **27** | 3-pyridyl | 63 | 307 | **32** | 2-furyl | 84 | 296 |
| **28** | 4-pyridyl | | no product | **33** | 3-furyl | 89 | 296 |
| **29** | 2-imidazolyl | 31 | 296 | **34** | 2-pyrrolyl | | no product |
| **30** | 4-imidazolyl | | no product | **35** | 3-(N-Me)indolyl | | no product |

rather than lack of reactivity of the aldehyde. In contrast, electron-donating substituents on the benzaldehyde can influence the reaction greatly and the positioning of the substituent can be important. A series of Mannich adducts derived from simple isomeric methoxybenzaldehydes is illustrative. High yields of pure adduct were obtained in the cases of 2-methoxy and 3-methoxybenzaldehyde (**18** and **19**), whereas 4-methoxybenzaldehyde was unreactive (entry 20). Similarly, vanillin, which also bears a strong electron-donating group in the para position, failed to react (entry 22), whereas the Mannich adduct of 3-hydroxybenzaldehyde was readily formed (**21**). In these cases, the electron-donating properties of the alkoxy substituent hinder Mannich adduct formation presumably because of inefficient iminium formation or, perhaps, instability of the iminium species under the reaction conditions.

A series of heterocyclic aldehydes was also examined, and a parallel trend emerged. Specifically, 3-pyridine carboxaldehyde, 2-furaldehyde, and 3-furaldehyde reacted smoothly to give the desired adducts (**27**, **32**, and **33** respectively). However, 2-pyridine (entry 26) and 4-pyridine carboxaldehydes (entry 28), as well as imidazole carboxamides, pyrrole carboxamides, quinoline carboxamides, and indole carboxamides were unsuitable substrates (entries 30, 34, 31, and 35, respectively) and no product was detected. A single exception, that of 2-imidazole carboxaldehyde, gave only minor amounts of impure product (**29**). These results may be attributed to resonance or inductive effects of the heteroatom, which deactivates the aldehyde center by reducing its electrophilicity. In such cases, formation of the incipient iminium species is compromised and addition of the alkyne component is prevented. However, if the heteroatom is sufficiently separated from the aldehyde center to minimize inductive effects and if resonance effects are precluded, then the aldehyde center is sufficiently reactive to generate the necessary iminium intermediate, and hence, the Mannich adduct is formed (Table 1).

## Conclusions

Solid-phase Mannich condensations of amines, aldehydes, and terminal alkynes, a multicomponent reaction, are a powerful synthetic methodology. A systematic investigation of aldehyde inputs has demonstrated that in general, aralkyl, aryl, and heteroaryl aldehydes are suitable substrates and give good yields of Mannich adduct of high purity. However, benzaldehydes bearing electron-donating substituents that decrease the electrophilicity of the carbonyl center, or heteroaryl aldehydes that are similarly deactivated via resonance effects, do not undergo reaction.

## Experimental Section

**General.** Reactions were performed in 3 separate blocks of 12 reactions each using glass-fritted screw-capped glass reaction vessels (1.5 cm × 8 cm, ~13 mL volume, made by Atmar Glass Co., Kennett Square, PA). Into a flask was placed 0.94 g of the resin-bound propargylamine (2-Cl Trityl resin, theoretical loading of 1.30 mmol/g),[8] and the material was suspended by adding a mixture of *N*,*N*-dimethylformamide (DMF) (7.5 mL) and dichloroethane (DCE) (17.5 mL). The mixture was physically agitated until it appeared as a homogeneous suspension. The suspension (which did not settle) was then divided equally (by volume using a wide-bore pipet) into 12 separate reaction tubes (theoretical load: 0.10 mmol propargylamine per tube). In each case, the solvent was pulled off under vacuum and the resin was rinsed with dichloromethane (DCM) (2 × 4 mL) and air-dried. Copper(I) chloride (10−14 mg, 1.0−1.5 equiv) was added to each reaction tube followed by dioxane (3 mL). A solution of phenylpiperazine in dioxane (1 M) was separately prepared, and 1 mL of this solution (1.0 mmol, 10 equiv) was added to each of the reaction vessels followed by the respective neat aldehyde (2.0 mmol, 20 equiv). The reaction vessels were then capped and heated (2 × 6 block custom-made by J-Kem Scientific, St. Louis, MO; heated with a temperature controller) while mixing, using an orbital shaker, at 75 °C for 4.5 h.

At this time, all liquids were pulled from each reaction vessel under vacuum and the remaining resin was washed with 10% piperidine/DMF (6 × 4 mL), DMF (2 × 4 mL), 50% water/DMF (4 × 4 mL), DMF (2 × 4 mL), and DCM (6 × 4 mL). The resin was air-dried, and the product was cleaved from the resin into preweighed tubes by treatment

with 25% TFA/DCM (4 mL) for 1 min followed by rinsing with DCM (2 × 2 mL). The solutions were subsequently warmed at 50 °C and dried under a stream of nitrogen. Acetonitrile (2 mL) was then added to each tube, and again, solvents were removed under a steady stream of nitrogen. The resulting residues were dried at 50 °C under vacuum overnight, weighed to calculate the mass of the product, and then analyzed for purity (HPLC, MS, and NMR). The products, as trifluoroacetate salts, were obtained as glassy brown semisolids that contained trace residual acetonitrile and water as evident by NMR.

Purity was determined by reverse-phase HPLC (Hewlett-Packard HP1100) using an acetonitrile/water gradient (10:90 to 90:10 v/v, with 0.1% TFA with a run time of 4 min) on a Supelcosil ABZ+Plus column (5 cm × 2.1 mm, 3 $\mu$m) operating at a flow rate of 0.75 mL/min; analysis was conducted at 220 nM wavelength, and retention times were recorded. Molecular parent ion identity was confirmed via mass spectrometry (Micromass Platform LC) using electrospray ionization and a probe voltage of 4.0 kV or on a Hewlett-Packard HP5989 MS engine using particle beam chemical ionization with ammonia as reagent gas. The structure of each final product was determined by nuclear magnetic resonance (Bruker AC-300SB FT-NMR) equipped with a 5 mm $^1H/^{13}C$ dual probe using DMSO-$d_6$ or $CD_3OD$ for fixed-frequency lock and chemical shift. Supporting data along with isolated yields for each final product are provided below.

**Compounds. 4-(4-Phenylpiperazin-1-yl)but-2-ynylamine (1).** $C_{14}H_{19}N_4$·3TFA, 571.39 (229.33). Yield = 67 mg. Theoretical = 57 mg. HPLC: 83% @ 0.39 min. MS: $MH^+$ = 230. NMR: 7.28 (t, 2H), 7.04 (d, 2H), 6.97 (t, 1H), 4.27 (s, 2H), 3.97 (s, 2H), 3.66−3.21 (br m, 8H).

**4-Phenyl-4-(4-phenylpiperazin-1-yl)but-2-ynylamine (2).** $C_{20}H_{23}N_3$·3TFA, 647.49 (305.43). Yield = 85 mg. Theoretical = 65 mg. HPLC: 95% @ 1.42 min. MS: $MH^+$ = 306. NMR: 7.71 (m, 2H), 7.54 (m, 3H), 7.32 (t, 2H), 7.09 (d, 2H), 7.01 (t, 1H), 5.63 (s, 1H), 4.08 (s, 2H), 3.62−3.26 (br m, 8H).

**5-(Phenyl)-4-(4-phenylpiperazin-1-yl)pent-2-ynylamine (3).** $C_{21}H_{25}N_3$·3TFA, 661.51 (319.45). Yield = 94 mg. Theoretical = 66 mg. HPLC: 96% @ 1.36 min. MS: $MH^+$ = 320. NMR: 7.37 (m, 7H), 7.09 (d, 2H), 6.99 (t, 1H), 4.68 (dd, 1H), 3.92 (s, 2H), 3.78−3.43 (br m, 8H), 3.39 (dd, 1H), 3.18 (t, 1H).

**5,5-Bis(phenyl)-4-(4-phenylpiperazin-1-yl)pent-2-ynylamine (4).** $C_{27}H_{29}N_3$·3TFA, 737.61 (395.55). Yield = 94 mg. Theoretical = 74 mg. HPLC: 93% @ 2.53 min. MS: $MH^+$ = 396. NMR: 7.50−7.12 (m, 15H), 4.88 (d, 1H), 4.43 (d, 1H), 3.78 (s, 2H), 3.59−3.15 (m, 8H).

**4-Cyclohexyl-4-(4-phenylpiperazin-1-yl)but-2-ynylamine (5).** $C_{20}H_{29}N_3$·3TFA, 653.53 (311.47). Yield = 85 mg. Theoretical = 65 mg. HPLC: 96% @ 1.69 min. MS: $MH^+$ = 312. NMR: 7.33 (t, 2H), 7.09 (d, 2H), 6.99 (t, 1H), 4.20 (d, 1H), 3.99 (s, 2H), 3.72−3.33 (br m, 8H), 2.12−1.93 (br m, 2H), 1.92−1.68 (br m, 4H), 1.49−1.16 (br m, 5H).

**(*E*)-6-(Phenyl)-4-(4-phenylpiperazin-1-yl)hex-5-en-2-ynylamine (6).** $C_{22}H_{25}N_3$·3TFA, 673.52 (331.46). Yield = 96 mg. Theoretical = 69 mg. HPLC: 63% @ 2.24 min. MS: $MH^+$ = 332. NMR: 7.57 (m, 2H), 7.40 (m, 3H), 7.32 (t, 2H), 7.16 (d, 1H), 7.08 (d, 2H), 7.00 (t, 1H), 6.39 (dd, 1H), 5.29 (d, 1H), 4.06 (s, 2H), 3.74−3.12 (br m, 8H).

**4-(2-Chlorophenyl)-4-(4-phenylpiperazin-1-yl)but-2-ynylamine (7).** $C_{20}H_{22}ClN_3$·3TFA, 681.93 (339.87). Yield = 39 mg. Theoretical = 68 mg. HPLC: 91% @ 2.13 min. MS: $MH^+$ = 340. NMR: 7.86 (m, 1H), 7.52 (m, 1H), 7.43 (m, 2H), 7.38 (d, 2H), 7.28 (d, 2H), 7.14 (t, 1H), 5.49 (s, 1H), 3.99 (s, 2H), 3.58−3.33 (br m, 4H), 3.32−3.09 (m, 4H).

**4-(3-Chlorophenyl)-4-(4-phenylpiperazin-1-yl)but-2-ynylamine (8).** $C_{20}H_{22}ClN_3$·3TFA, 681.93 (339.87). Yield = 79 mg. Theoretical = 68 mg. HPLC: 92% @ 2.19 min. MS: $MH^+$ = 340. NMR: 7.72 (s, 1H), 7.62 (m, 1H), 7.49 (m, 2H), 7.37 (t, 2H), 7.22 (d, 2H), 7.12 (t, 1H), 5.42 (s, 1H), 4.04 (s, 2H), 3.62−3.42 (br m, 4H), 3.41−3.18 (m, 4H).

**4-(4-Chlorophenyl)-4-(4-phenylpiperazin-1-yl)but-2-ynylamine (9).** $C_{20}H_{22}ClN_3$·3TFA, 681.93 (339.87). Yield = 85 mg. Theoretical = 68 mg. HPLC: 94% @ 2.22 min. MS: $MH^+$ = 340. NMR: 7.68 (d, 2H), 7.52 (d, 2H), 7.35 (t, 2H), 7.18 (d, 2H), 7.08 (t, 1H), 5.49 (s, 1H), 4.04 (s, 2H), 3.59−3.42 (br m, 4H), 3.41−3.20 (m, 4H).

**4-(2,4-Dichlorophenyl)-4-(4-phenylpiperazin-1-yl)but-2-ynylamine (10).** $C_{20}H_{21}Cl_2N_3$·3TFA, 716.38 (374.32). Yield = 79 mg. Theoretical = 72 mg. HPLC: 90% @ 2.53 min. MS: $MH^+$ = 374. NMR: 7.80 (d, 1H), 7.60 (s, 1H), 7.49−7.34 (m, 5H), 7.24 (t, 1H), 5.34 (s, 1H), 3.99 (s, 2H), 3.62−3.33 (br m, 4H), 3.13 (m, 4H).

**4-(2-Trifluorophenyl)-4-(4-phenylpiperazin-1-yl)but-2-ynylamine (11).** $C_{21}H_{22}F_3N_3$·3TFA, 715.48 (373.42). Yield = 64 mg. Theoretical = 72 mg. HPLC: 89% @ 2.48 min. MS: $MH^+$ = 374. NMR: 8.06 (d, 1H), 7.79 (d, 1H), 7.72 (t, 1H), 7.60 (t, 1H), 7.45 (t, 2H), 7.38 (d, 2H), 7.23 (t, 1H), 5.12 (s, 1H), 3.96 (s, 2H), 3.62−3.24 (br m, 4H), 3.14 (m, 2H), 2.99 (m, 2H).

**4-(3-Trifluorophenyl)-4-(4-phenylpiperazin-1-yl)but-2-ynylamine (12).** $C_{21}H_{22}F_3N_3$·3TFA, 715.48 (373.42). Yield = 74 mg. Theoretical = 72 mg. HPLC: 87% @ 2.43 min. MS: $MH^+$ = 374. NMR: 7.97 (m, 2H), 7.78 (d, 1H), 7.70 (t, 1H), 7.41 (t, 2H), 7.29 (d, 2H), 7.17 (t, 1H), 5.44 (s, 1H), 4.04 (s, 2H), 3.55 (br m, 4H), 3.28 (m, 4H).

**4-(4-Trifluorophenyl)-4-(4-phenylpiperazin-1-yl)but-2-ynylamine (13).** $C_{21}H_{22}F_3N_3$·3TFA, 715.48 (373.42). Yield = 81 mg. Theoretical = 72 mg. HPLC: 91% @ 2.47 min. MS: $MH^+$ = 374. NMR: 7.90 (d, 2H), 7.79 (d, 2H), 7.40 (t, 2H), 7.28 (d, 2H), 7.17 (t, 1H), 5.40 (s, 1H), 4.05 (s, 2H), 3.52 (br m, 4H), 3.22 (m, 4H).

**4-(2-Methylphenyl)-4-(4-phenylpiperazin-1-yl)but-2-ynylamine (15).** $C_{21}H_{25}N_3$·3TFA, 661.51 (319.45). Yield = 71 mg. Theoretical = 66 mg. HPLC: 95% @ 2.04 min. MS: $MH^+$ = 320. NMR: 7.73 (d, 1H), 7.36 (m, 5H), 7.19 (d, 2H), 7.10 (t, 1H), 5.47 (s, 1H), 4.02 (s, 2H), 3.56−3.19 (br m, 8H), 2.50 (s, 3H).

**4-(3-Methylphenyl)-4-(4-phenylpiperazin-1-yl)but-2-ynylamine (16).** $C_{21}H_{25}N_3$·3TFA, 661.51 (319.45). Yield = 81 mg. Theoretical = 66 mg. HPLC: 93% @ 2.09 min. MS: $MH^+$ = 320. NMR: 7.56−7.36 (m, 4H), 7.30 (t, 2H), 7.07 (d, 2H), 6.99 (t, 1H), 5.57 (s, 1H), 4.06 (s, 2H), 3.60−3.28 (br m, 8H), 2.42 (s, 3H).

**4-(4-Methylphenyl)-4-(4-phenylpiperazin-1-yl)but-2-ynylamine (17).** $C_{21}H_{25}N_3$·3TFA, 661.51 (319.45). Yield = 76 mg. Theoretical = 66 mg. HPLC: 93% @ 2.09 min. MS: $MH^+$ = 320. NMR: 7.59 (d, 2H), 7.38 (d, 2H), 7.30 (t, 2H), 7.07 (d, 2H), 6.98 (t, 1H), 5.61 (s, 1H), 4.05 (s, 2H), 3.62−3.23 (br m, 8H), 2.42 (s, 3H).

**4-(2-Methoxyphenyl)-4-(4-phenylpiperazin-1-yl)but-2-ynylamine (18).** $C_{21}H_{25}N_3O$·3TFA, 677.51 (335.45). Yield = 77 mg. Theoretical = 68 mg. HPLC: 93% @ 1.87 min. MS: $MH^+$ = 336. NMR: 7.74 (d, 1H), 7.58 (t, 1H), 7.30 (t, 2H), 7.18 (m, 2H), 7.02 (d, 2H), 6.95 (t, 1H), 5.92 (s, 1H), 4.03 (s, 2H), 3.98 (s, 3H), 3.68−3.32 (br m, 8H).

**4-(3-Methoxyphenyl)-4-(4-phenylpiperazin-1-yl)but-2-ynylamine (19).** $C_{21}H_{25}N_3O$·3TFA, 677.51 (335.45). Yield = 85 mg. Theoretical = 68 mg. HPLC: 92% @ 1.95 min. MS: $MH^+$ = 336. NMR: 7.46 (t, 1H), 7.37−7.22 (m, 4H), 7.11 (m, 3H), 7.01 (t, 1H), 5.58 (s, 1H), 4.06 (s, 2H), 3.87 (s, 3H), 3.62−3.33 (br m, 8H).

**4-(3-Hydroxyphenyl)-4-(4-phenylpiperazin-1-yl)but-2-ynylamine (21).** $C_{20}H_{23}N_3O$·3TFA, 662.49 (321.43). Yield = 90 mg. Theoretical = 66 mg. HPLC: 92% @ 0.97 min. MS: $MH^+$ = 322. NMR: 7.39−7.22 (m, 3H), 7.16−6.89 (m, 6H), 5.55 (s, 1H), 4.05 (s, 2H), 3.63−3.23 (br m, 8H).

**4-(4-Phenylphenyl)-4-(4-phenylpiperazin-1-yl)but-2-ynylamine (23).** $C_{26}H_{27}N_3$·3TFA, 723.59 (381.53). Yield = 90 mg. Theoretical = 72 mg. HPLC: 94% @ 2.58 min. MS: $MH^+$ = 382. NMR: 7.79 (s, 4H), 7.68 (d, 2H), 7.49 (t, 2H), 7.41 (d, 1H), 7.32 (t, 2H), 7.11 (d, 2H), 7.02 (t, 1H), 5.67 (s, 1H), 4.08 (s, 2H), 3.63−3.33 (br m, 8H).

**4-(1-Naphthyl)-4-(4-phenylpiperazin-1-yl)but-2-ynylamine (24).** $C_{24}H_{25}N_3$·3TFA, 697.55 (355.49). Yield = 74 mg. Theoretical = 70 mg. HPLC: 95% @ 2.40 min. MS: $MH^+$ = 356. NMR: 8.35 (d, 1H), 7.99 (m, 3H), 7.62 (m, 3H), 7.38 (t, 2H), 7.28 (d, 2H), 7.18 (t, 1H), 6.09 (s, 1H), 4.07 (s, 2H), 3.65−3.19 (br m, 8H).

**4-(2-Naphthyl)-4-(4-phenylpiperazin-1-yl)-but-2-ynylamine (25).** $C_{24}H_{25}N_3$·3TFA, 697.55 (355.49). Yield = 85 mg. Theoretical = 70 mg. HPLC: 91% @ 2.38 min. MS: $MH^+$ = 356. NMR: 8.22 (s, 1H), 8.04 (d, 1H), 7.98 (m, 2H), 7.78 (d, 1H), 7.62 (m, 2H), 7.32 (t, 2H), 7.10 (d, 2H), 7.01 (t, 1H), 5.77 (s, 1H), 4.11 (s, 2H), 3.68−3.25 (br m, 8H).

**4-(3-Pyridyl)-4-(4-phenylpiperazin-1-yl)but-2-ynylamine (27).** $C_{19}H_{22}N_4$·3TFA, 762.49 (306.41). Yield = 68 mg. Theoretical = 76 mg. HPLC: mixture, 31% @ 0.32 min and 63% @ 0.50 min (product). MS: $MH^+$ = 307. NMR: mixture.

**4-(2-Imidazolyl)-4-(4-phenylpiperazin-1-yl)but-2-ynylamine (29).** $C_{17}H_{21}N_5$·4TFA, 751.47 (295.39). Yield = 50 mg. Theoretical = 75 mg. HPLC: mixture, 40% @ 0.22 min, 29% @ 0.27 min and 31% @ 0.50 min (product). MS: $MH^+$ = 296. NMR: mixture.

**4-(2-Furyl)-4-(4-phenylpiperazin-1-yl)but-2-ynylamine (32).** $C_{18}H_{21}N_3O$·3TFA, 637.45 (295.39). Yield = 69 mg. Theoretical = 64 mg. HPLC: 84% @ 0.72 min. MS: $MH^+$ = 296. NMR: 7.69 (d, 1H), 7.33 (t, 2H), 7.12 (d, 2H), 7.05 (t, 1H), 6.83 (d, 1H), 6.58 (t, 1H), 5.68 (s, 1H), 4.02 (s, 2H), 3.58−3.05 (br m, 8H).

**4-(3-Furyl)-4-(4-phenylpiperazin-1-yl)but-2-ynylamine (33).** $C_{18}H_{21}N_3O$·3TFA, 637.45 (295.39). Yield = 91 mg. Theoretical = 64 mg. HPLC: 89% @ 0.71 min. MS: $MH^+$ = 296. NMR: 7.92 (s, 1H), 7.69 (s, 1H), 7.33 (t, 2H), 7.09 (d, 2H), 7.00 (t, 1H), 6.75 (s, 1H), 5.67 (s, 1H), 4.04 (s, 2H), 3.49 (br s, 8H).

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**Supporting Information Available.** Spectra and listing of additional data for the compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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CC0100161