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Convenient and efficient synthesis of disubstituted piperazine derivatives by catalyst-free, atom-economical and tricomponent domino reactions

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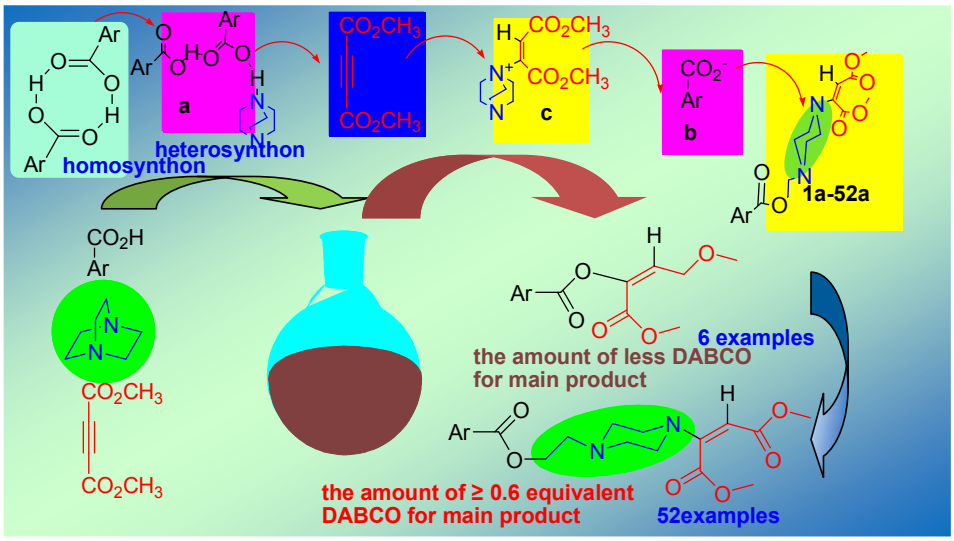
catalyst-free •one-pot•disubstituted piperazine derivatives • tri-component domino reaction• diversity-oriented synthesis • atom economy

One-pot, atom-economical, catalyst-free and tri-component domino reactions are applied to diversity-oriented synthesis (DOS) of disubstituted piperazine derivatives under mild conditions with moderate to high yields. This protocol exhibits potential applicability in the synthesis of pharmaceuticals, liquid crystals, complexes, etc. Because of its operational simplicity and convenience, it may be suitable for application in large-scale synthesis.



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Convenient and efficient synthesis of disubstituted piperazine derivatives by catalyst-free, atom-economical and tricomponent domino reactions

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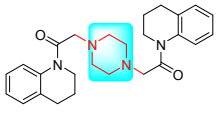
One-pot, atom-economical, catalyst-free and tri-component domino reactions are applied to diversity-oriented synthesis (DOS) of disubstituted piperazine derivatives under mild conditions with moderate to high yields. This protocol exhibits potential applicability in the synthesis of pharmaceuticals, liquid crystals, complexes, etc. Because of its operational simplicity and convenience, it may be suitable for application in large-scale synthesis.

Some reactions and synthetic methodologys, for example cascade, tandem, one-pot, multicomponent domino reactions, atom-economical, catalyst-free, ring opening, supramolecular self-assembly, diversity-oriented synthesis (DOS) and functional-oriented synthesis (FOS), are increasingly applied to the construction of natural and designed molecules. Such processes, in which ideally a single event triggers the conversion of a starting material to a product which then becomes a substrate for the next reaction until termination leads to a stable final product, are highly desirable not only due to their elegance, but also because of their efficiency and economy in terms of reagent consumption and purification. Often, these one-pot multistep procedures are accompanied by dramatic increases in molecular complexity and impressive selectivity. The discovery of new molecular diversity from nature and the demand for more efficient and environmentally benign chemical processes dictates and invites the further development of such synthetic strategies and tactics as we move into a new age of chemical synthesis.[1]

Piperazine ring and its derivatives present in many nature products, such as anticancer Aspernigerin(**Scheme 1**), etc.[2]



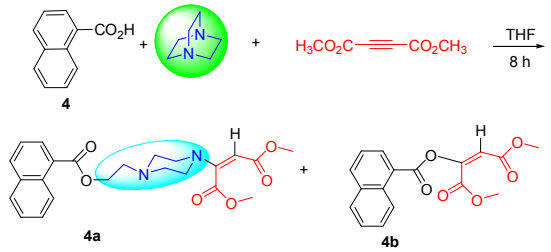
Scheme 1. Aspernigerin

The new classes of hybrid anticancer drugs were obtained by selective functionalization of the piperazine scaffold following fragment-based drug design. The piperazine nucleus and its substituted products play an important role in anticancer (The invention compounds are useful for the treatment of cancers including glioblastomas, lung cancers, colon cancers, gastric(stomach) cancer, breast cancer, esophageal cancer, and prostate cancer, liver cancer, breast cancer, leukemia, lymphoma, kidney cancer, skin cancer, pancreatic cancer...) activity[3] and pharmacological properties. The arylpiperazine framework is observed in agreat deal of compounds of pharmaceutical interest. In 2001, the MDDR (MDL Drug Data Report) listed 2271 phenylpiperazines which totaled 65 structures in clinical trials or higher across 23 therapeutic areas.[4] The piperazine or piperazinone core also presents in the compounds that are possessing anti-fungal, anti-depressant, anti-malarial, anti-migraine, anti-diabetic, anti-thrombotic, anti-aggregating, etc. [5] Piperazine derivatives are important intermediates in organic synthesis and can be used as the building blocks in pharmaceutical and fine chemical industries. Some disubstituted piperazine derivatives are applications in liquid crystals, [6] complexe, [7] coatings, sealing materials, adhesives and hot-melt adhesive, [8] self-assembled monolayer in an electronic device, [9] novel charge-transfer polymers in solar cells et al, [10] non-aqueous gel ion conductor compositions used in batteries, [11] self-assembly of supra-molecular polymer materials, [12] antistatic agents and vulcanization accelerators, [13] etc.

Aromatic ring, aromatic heterocyclic ring and its derivatives are the parent structure of many nature products. Most of the heterocyclic nucleuses use exhibit remarkable pharmacological activities. The new classes of hybrid derivatives were obtained by selective of the heterocyclic ring scaffold. The 1*H*-1,2,3-triazole derivative is a heterocyclic compounds with wide biological activity and applications in many fields.[14] The triazole ring nucleus also exhibits remarkable pharmacological activities and selective functionalization of the heterocyclic ring scaffold.[15] Amino acid is the smallest unit formation of protein and polypeptide, and the

most of amino acids was chiral. Some amino acids are used for important chiral tool sources in chiral synthesis or asymmetric synthesis. Proteins and peptides are chiral, enzyme and cell is also composed of chiral proteins. The cancer or some diseases is caused by some enzymes or cells. Hence, to inhibit these enzymes or cells, the chiral drugs was required.

In the one-pot, atom-economical, catalyst-free, supra-molecular homo- and hetero-synthon, ring opening and tri-component domino reactions are being applied to the diversity-oriented synthesis and construction progress of designed molecules. In the processes, the conversion of a starting material to a product is highly desirable, efficient and economic in terms of reagent consumption and purification. These multistep, one-pot procedures are accompanied by dramatic increases in molecular complexity and impressive selectivity, and are suitable for application in scale the synthesis. To examine the yield of diversity-oriented synthesis (DOS), atom-economical, one-pot and tri-component domino reactions, we chose the 1-naphthoic acid (**4**), dimethyl acetylene dicarboxylate (DMAD) as a model substrate. The yield of **4a** and **4b** is examined by the change of 1,4-diazabicyclo[2.2.2]octane (DABCO) mol%. Finally result shows, when the amount of DABCO is less, it is a catalyst and main product **4b** is obtained. When the amount of DABCO is more than 0.6 equivalent, it acts as a reactant and gives major product **4a**. The reaction is shown in **Scheme 2.** The results of the reaction using different amount of DABCO are shown in **Figure 1**.



Scheme 2. Synthesis conditions of title compound **4a**.

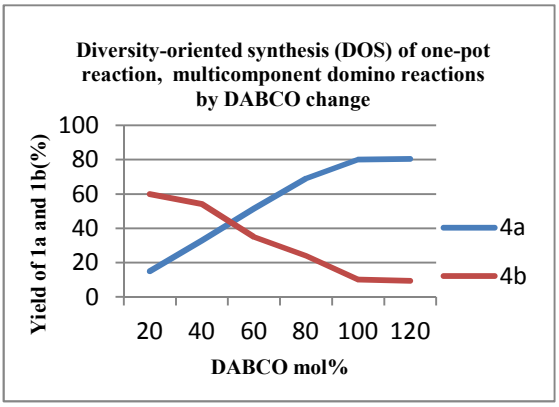
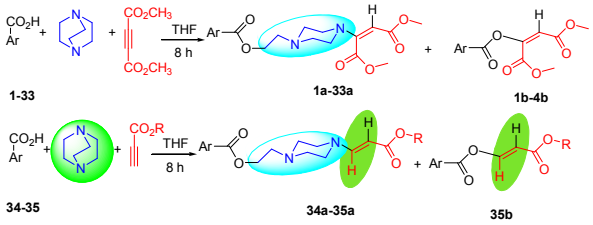


Figure 1. The yield of title compound **4a** is changed by quantity of DABCO added.

The new class derivatives for selective functionalization of the aromatic ring scaffold. Some novel disubstituted piperazine derivatives were synthesized by substituted aromatic acids(**Table 1**).

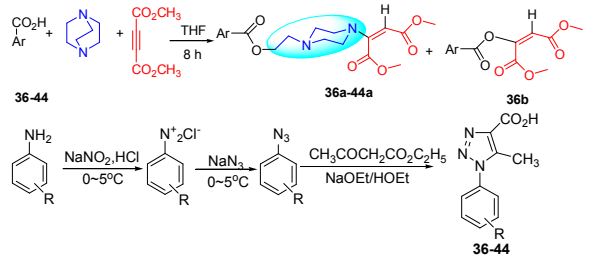
Table 1 Synthesis of some novel aryl piperazine derivatives



Entry	Ar-COOH	Yields(%)
1	4-Br-C_6H_4-COOH	1a 86%
		1b 11%
2	2-Cl-C_6H_4-COOH	2a 86%
		2b 9%
3	*β*- $C_{10}H_7$-OCH_2COOH	3a 72%
		3b 16%
4	*α*- $C_{10}H_7$-COOH	4a 82%
		4b 12%
5	*α*- $C_{10}H_7$-CH_2COOH	5a 62%
6	2-CH_3COO-C_6H_4-COOH	6a 43%
7	4-F-C_6H_4-COOH	7a 89%
8	Ph-CH=CH-COOH	8a 59%
9	4-NC-C_6H_4-COOH	9a 57%
10	4-CH_3O-C_6H_4-COOH	10a 75%
11	Ph-CH(OH)-COOH	11a 79%
12	2-Br-C_6H_4-COOH	12a 84%
13	2-CH_3O-C_6H_4-COOH	13a 64%
14	3-CH_3O-C_6H_4-COOH	14a 74%
15	3-Cl-C_6H_4-COOH	15a 85%
16	2-F-C_6H_4-COOH	16a 81%
17	3-CH_3-C_6H_4-COOH	17a 75%
18	Ph-COOH	18a 89%
19	Ph-CH_2COOH	19a 74%
20	3-CH_3-C_6H_4-COOH	20a 66%
21	2,4-DiCl-C_6H_3-OCH_2COOH	21a 69%
22	C_6H_3-OCH_2COOH	22a 72%
23	*α*- $C_{10}H_7$-OCH_2COOH	23a 75%
24	4-I-C_6H_4-COOH	24a 74%
25	2-I-C_6H_4-COOH	25a 65%
26	2-CH_3COO-C_6H_4-COOH	26a 31%
27	Nicotinic acid	27a 68%
28	5-Bromopyridine-3-COOH	28a 89%
29	Quinoline-2-COOH	29a 71%
30	Pyrazine-2-COOH	30a 66%
31	(Tetrazol-1-yl)acetic acid	31a 55%
32	Furan-2-COOH	32a 79%
33	Picolinic acid	33a 77%
34	4-Br-C_6H_4-COOH,R=-CH_3	34a 45%
35	4-Br-C_6H_4-COOH,R= -Et	35a 39%
		35b 25%

Some novel disubstituted piperazine derivatives were synthesized by substituted 1,2,3-triazolyl acids (**Table 2**).

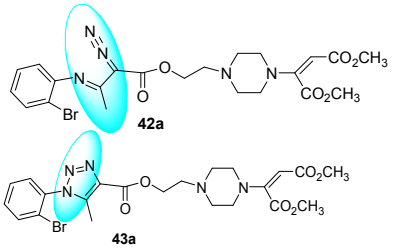
Table 2 Synthesis of some novel 1*H*-1,2,3-triazolyl piperazine derivatives



Entry	Ar-COOH	Yields(%)
36	1-(4-Chlorophenyl)-5-methyl-1*H*-1,2,3-triazole-4-carboxylic acid	36a 68% 36b 25%
37	5-Methyl-1-phenyl-1*H*-1,2,3-triazole-4-carboxylic acid	37a 71%
38	1-(4-Ethoxyphenyl)-5-methyl-1*H*-1,2,3-triazole-4-carboxylic acid	38a 64%
39	5-Methyl-1-(naphthalen-2-yl)-1*H*-1,2,3-triazole-4-carboxylic acid	39a 82%
40	1-(4-Methoxyphenyl)-5-methyl-1*H*- 1,2,3-	40a 60%

	triazole-4-carboxylic acid	
41	1-(4-Chlorophenyl)-5-methoxy-1*H*- 1,2,3-triazole-4-carboxylic acid	**36a 63%**
42	1-(2-Bromophenyl)-5-methyl-1*H*-1,2,3-triazole-4-carboxylic acid	**42a 35%**
43	1-(2-Bromophenyl)-5-methyl-1*H*-1,2,3-triazole-4-carboxylic acid	**43a 49%**
44	1-(3-Chlorophenyl)-5-methyl-1*H*-1,2,3-triazole-4-carboxylic acid	**44a 67%**

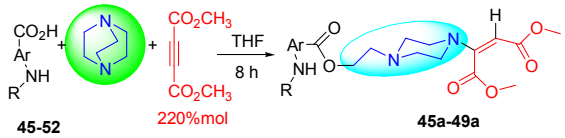
When 1-[1-(1-aryl-5-methyl-1*H*-1,2,3-triazole-4-carboyloxyl) ethan-2-yl]-4-[(*E*)-1,2-(dimethoxycarbonyl)ethen-1-yl]piperazine derivatives were synthesized, novel compounds **42a** and **43a** were obtained by the reaction of 1-(2-bromophenyl)-5-methyl-1*H*-1,2,3-triazole-4-carboxylic acid, DABCO, dimethyl but-2-ynedioate. Compound **43a** is a normal product, but 1-{2-[2-diazo-3-(*E*)-(2-bromophenylimino)butyroyloxyl]ethan-1-yl}-4-[(dimethoxycarbonyl) -ethen-1-yl] piperaine **42a** is a compound involving diazo compound by showing strong IR absorption at 2125 cm^{-1}.[16] The structures are shown in **Scheme 3**.

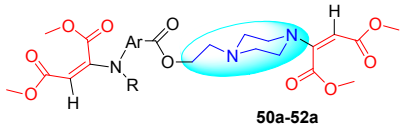


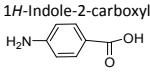
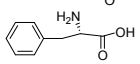
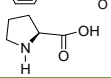
Scheme 3. The target compound**42a** and **43a**.

Some target compounds were synthesized by amino acid or substituted amino acid. The reaction is shown in **Table 3**.

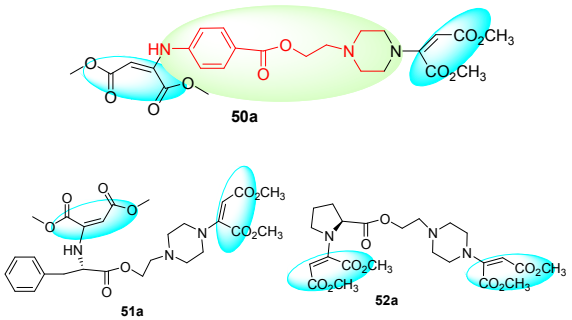
Table 3 Synthesis of some novel (un)substituted amino carboxylic acid piperazine derivatives





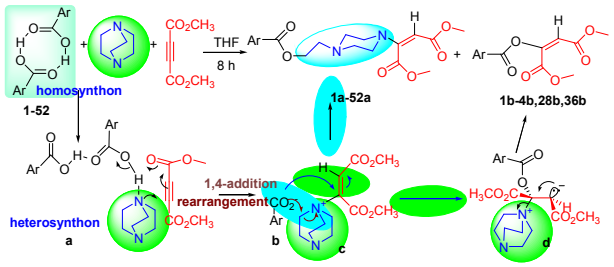
Entry	Ar-COOH	Yields(%)
45	2-(Phenylamino)benzoic acid	**45a 89%**
46	(±)-5-Oxopyrrolidine-2-carboxylic acid	**46a 68%**
47	2-(Benzamido)acetic acid	**47a 90%**
48	2-(1*H*-Indol-3-yl)acetic acid	**48a 61%**
49	1*H*-Indole-2-carboxylic acid	**49a 77%**
50		**50a 69%**
51		**51a 55%**
52		**52a 78%**

When the target compounds were synthesized by some amino carboxylic acid, the products with bis(*E*)-1,2-(dimethoxycarbonyl) ethen-1-yl compounds **50a**, **51a** and **52a** were obtained (**Scheme 4**).



Scheme 4. The target compound **50a**, **51a** and **52a**.

A proposed mechanism of this reaction is shown (in **Scheme 7**) based on the previous investigation.[17] Initially, reaction of Ar-COOH (dimeric supra-mol. homo-synthon) **1** and DABCO form a DABCO aromatic acid salt (supra-mol. hetero-synthon) **a**. Then, an intermolecular nucleophilic addition reaction of hetero-synthon **a** attacks DMAD was happened and the corresponding zwitterionic intermediate **b** and **c** were given. When the aromatic acid anion **b** attacks DABCO cationic intermediate **c,** a reaction of nucleophilic substitution was reacted and the final products **1a-52a** is obtained. If reaction was Michael addition of anion **b** to intermediate **c**, zwitterionic intermediate **d** was given, then DABCO was eliminated from intermediate **d** to afford the final product **1b-4b**(**Scheme 5**).



Scheme 5. Plausible mechanism for the reaction

In order to prove the configuration of DMAD adduct, the compound **34a**, **35a** and **35b** are synthesized. It was good known that the C=C configuration can be proved by the adjacent hydrogen coupling constant of olefinic bond. The compound **34a**, **35a** and **35b** was *trans* configuration by the coupling constant of olefinic hydrogen, hence, the addition reaction of acetylene, DMAD and DABCO, which was proved for *cis* adducted. In the meantime, the C=C configuration for *cis* adducts and piperazine ring conformation is also confirmed by crystalline structure of the target compounds **40a**. The crystal structure of compound **40a** is shown in **Figure 2.** The supra-molecular structure of compound **40a** is shown in **Figure 3.**

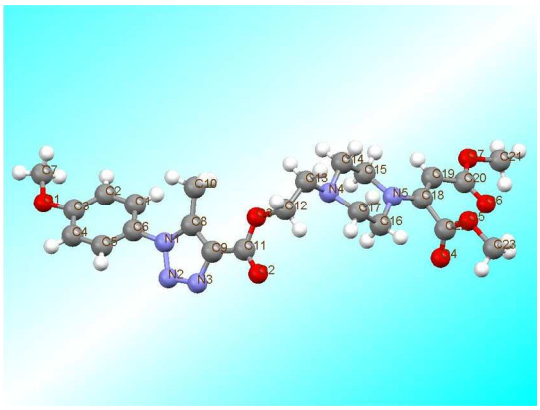


Figure 2. A Mercury (CCDC, 2005) view of the molecular structure of **40a**(CCDC No: 1019130).

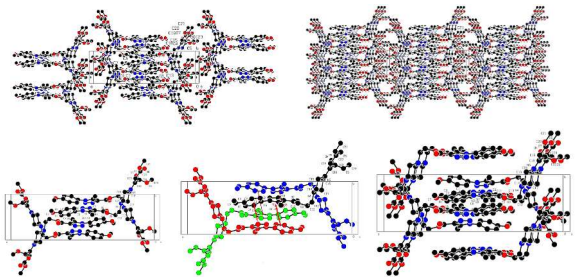


Figure 3. The π-π accumulation structure of **40a** supra-molecular.

In summary, catalyst-free, one-pot, atom-economical, supra-molecular homo- and hetero-synthon, ring opening and tri-component domino reactions are applied to diversity-oriented synthesis (DOS) of disubstituted piperazine derivatives under mild conditions with moderate to high yields. This protocol exhibits potential applicability in the synthesis of pharmaceuticals and natural products, because of the operational simplicity, the convenient and available reactants. The target compounds are synthesized for an organic whole structure of procaine part and anticancer drugs heterocyclic compounds. We should point out that the target compounds is of low expenditure and novel in biological and pharmacological fields, and suitable for application in the industrial scale synthesis.

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Notes and references

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† Electronic Supplementary Information (ESI) available: Experimental procedure, characterization data, ^{1}H and ^{13}C NMR spectra, X-ray crystal data of products See DOI: 10.1039/b000000x/

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