# Triethylammonium acetate (*TEAA*): a recyclable inexpensive ionic liquid promotes the chemoselective aza- and thia-*Michael* reactions

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**Abstract** A new, highly efficient, inexpensive, recyclable, mild, convenient, and green protocol for chemoselective aza/thia-*Michael* addition reactions of amines/thiols to $\alpha,\beta$-unsaturated compounds using triethylammonium acetate (*TEAA*) ionic liquid was developed. The catalyst can be recycled ten times and obviate the need for toxic and expensive catalysts.

**Keywords** Triethylammonium acetate (*TEAA*); Green; Ionic liquid; Aza/thia-*Michael* reaction.

## Introduction

The *Michael* reaction has been studied for more than one century. The conjugate addition of amines to carbon–carbon double bonds is a useful protocol in synthetic organic chemistry [1]. It is used extensively in the synthesis of pharmaceutical intermediates, peptide analogues, antibiotics, and other biologically active molecules and drugs [2–4]. In the past few years, a number of alternative procedures have been developed for the conjugate addition of amines to $\alpha,\beta$-unsaturated nitriles and carbonyl compounds. In particular, various *Lewis* acid catalyzed reactions have been reported [5]. Recently, there were also some reports of this reaction conducted in Cu(*acac*)$_2$/

ionic liquid [6, 7], water [8], $\beta$-*CD* in water [9], cerium ammonium nitrate (*CAN*) [10], HClO$_4$–SiO$_2$ [11], *DBU* [12], neat [13], and indium(III) chloride [14]. Unfortunately, many of these processes suffer from limitations, such as the use of expensive reagents, harsh conditions, relatively long reaction times, high catalyst loading, low selectivity, presence of side reactions, and tedious work-up procedures for their separation, recycling, or disposal problems and effluent pollution. All these limitations forced us to explore a new catalyst, which has more efficiency and less limitation. So we tried to explore the new catalyst that has certain properties, such as good thermal and mechanical stabilities of supported reagents, is easy to handle, of low toxicity, non-corrosive, easy to separate from reaction mixture through filtration, and feasible for reuse.

Ionic liquids as new reaction media and catalysts have been experimentally and theoretically recognized and accepted [15]. The application of ionic liquids as novel media may provide convenient solutions to both the solvent emission and catalyst reuse problem [16]. A great deal of attention has been given to imidazolium ionic liquids in the past several years [17]. Recently, *Li-Wen Xu* and coworkers [18] have used basic ionic liquid [*bmim*][OH] to catalyze the aza-*Michael* reaction of aromatic amines in long reaction times of 8–24 h affording the addition product in 42–98% yields. However, industrial application of these ionic liquids is limiting because of the

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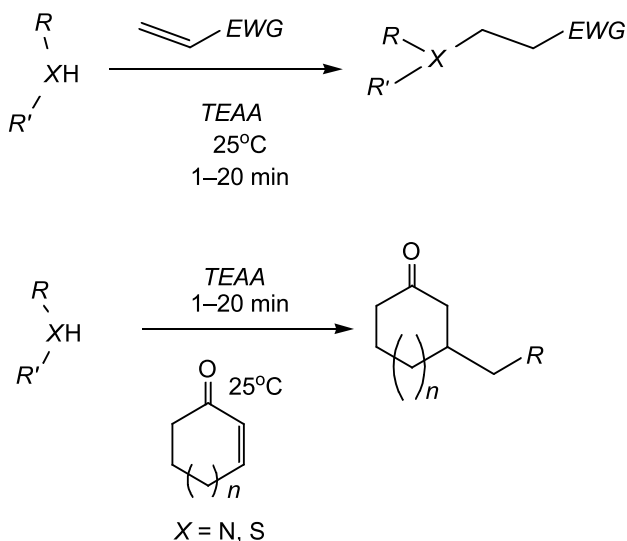
R, R′ = H, N-alkyl, N-arylpiperazines, aliphatic, aromatic, heterocycles.

EWG = CN, COOC$_2$H$_5$, COOCH$_3$, COCH$_3$

**Scheme 1**

high price of imidazolium ionic liquids and also due to low recyclability [19]. Low-cost ionic liquids, such as ammonium ionic liquids have drawn much attention in the recent time for their use in synthesis methodology. Recently, *Ganeshpure* and co-workers [20] used a simple ammonium ionic liquid for the *Fischer* esterification. By using this methodology we try to explore the aza/thia-*Michael* reaction using the triethylammonium acetate ionic liquid.

## Results and discussion

As a part of our research on developing on economical, environmentally friendly route for C–N and C–S bond forming reaction [21], herein we report the conjugate addition of amines and thiols to α,β-unsaturated nitriles and carbonyl compounds using the *TEAA* ionic liquid (Scheme 1).

The report by the *B.C. Ranu* group [8] showed the potential of water as the catalyst/reaction medium for the aza-*Michael* reaction with aliphatic amines, but with aromatic amines it was not successful. One more report by the *Gopal L. Khatik* group [8] showed the potential of water for thia-*Michael* reaction with simple substrates. However, there has been no straightforward synthesis of these uncomplicated enones (*e.g.*, chalcones, *trans*-4-phenyl-3-buten-2-one,
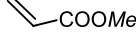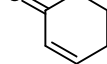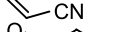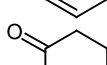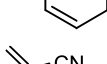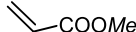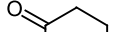
*etc.*), which cannot react in water even under forcible condition [11]. We designed a new protocol with *TEAA* as the catalyst/reaction medium system for carrying out the *Michael* reaction of amines and thiols with α,β-unsaturated compounds to obtain the desired products (minutes) with excellent yield and purity. The product with 1 mmol scale of reactands needed not any purification with column chromatography. *TEAA* when added as a reaction medium, the reaction rates as well as yields of the reaction improved dramatically. This is probably due to the higher solubility of amines/thiols in the ionic liquid. This protocol was successfully applied to catalyze the *Michael* addition of various substituted piperazines, aliphatic, aromatic amines, imidazoles, and thiols with α,β-unsaturated nitriles and carbonyl compounds. Results of the reactions are summarized in Tables 1 and 2. The (4-nitrophenyl)piperazine (**1g**), (4-amino-phenyl) piperazine (**1h**), and other substituted piperazines with various *Michael* acceptors, *i.e.*, acrylonitrile, methyl acrylate, and cyclohexenone at 25°C gave the corresponding adduct in excellent yields up to 99% after 1 min of addition of *TEAA* to the reaction system (Table 1).

The product thus formed was separated from the reaction mixture by extraction using diethyl ether. The product was formed in pure form without any side product and did not need any further purification. The reaction of aromatic amines, *e.g.*, anilines and various other substituted anilines, proceeded within 30 min after the addition of catalyst to the reaction system containing the *Michael* acceptor.

In order to extend the scope of this methodology, *N*-heterocycles **1v–1x**, *e.g.*, imidazole and substituted imidazoles were used for aza-*Michael* reaction with α,β-unsaturated compounds. It is noticed that the reaction took more time to complete (analysis by TLC and GC) as compared with other amines, which may be due to the steric hindrance in heterocycles. Similar to the aza-*Michael* reaction there is also dramatical increase in the reactivity and yield by addition of *TEAA* (Table 2).
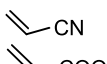
Thus, a probable mechanism for the reaction using *TEAA* as a catalyst for both the thia-*Michael* and the aza-*Michael* reaction due to the enhanced reactivity in the triethylammonium acetate ionic liquid attributed to the inherent *Brønsted* and *Lewis* acidily of the [$Et_3$NH]$^+$ cation, which makes the NH and SH bond weaker, enhancing the nucleo-

**Table 1** Aza-*Michael* reaction of amines with $\alpha,\beta$-unsaturated compounds catalyzed by [*Et*$_3$NH][CH$_3$COO] at room temperature

| Entry | Comp. | Amine | *Michael* accceptor | Time/min | Yield/%[b] | Ref. |
|---|---|---|---|---|---|---|
| 1 | **1a** | Piperazines (*Pip*) | CH$_2$=CH–CN | 1 | 99 | [21] |
| 2 | **1b** | 1-*MePip* | CH$_2$=CH–COO*Me* | 1 | 99 | [21] |
| 3 | **1c** | 1-*PhPip* | CH$_2$=CH–CN | 1 | 99 | [21] |
| 4 | **1d** | 1-*BhPip* | CH$_2$=CH–CN | 1 | 98 | [21] |
| 5 | **1e** | 1-*PhPip* | cyclohex-2-enone | 1 | 98[c] | |
| 6 | **1f** | 1-(4-Cl*Ph*)*Pip* | CH$_2$=CH–CN | 1 | 95[c] | |
| 7 | **1g** | 1-(4-NO$_2$*Ph*)*Pip* | CH$_2$=CH–CN | 1 | 96[c] | |
| 8 | **1h** | 1-(4-NH$_2$*Ph*)*Pip* | CH$_2$=CH–CN | 1 | 94[c] | |
| 9 | **1i** | 1-(*BDO* CH$_2$)*Pip*[a] | CH$_2$=CH–CN | 1 | 93[c] | |
| 10 | **1j** | 1-[2(*MeO*)*Ph*]*Pip* | CH$_2$=CH–CN | 1 | 98 | [21] |
| 11 | **1k** | 1-(2-*MePh*)*Pip* | CH$_2$=CH–CN | 1 | 97 | [21] |
| 12 | **1l** | (*n*-C$_4$H$_9$)$_2$NH | CH$_2$=CH–CN | 5 | 98 | [26] |
| 13 | **1m** | (*n*-C$_4$H$_9$)$_2$NH | CH$_2$=CH–COO*Et* | 5 | 98 | [26] |
| 14 | **1n** | Morpholine | CH$_2$=CH–CN | 1 | 96 | [26] |
| 15 | **1o** | Morpholine | cyclohex-2-enone | 1 | 97 | [26] |
| 16 | **1p** | *Ph*CH$_2$NH$_2$ | cyclohex-2-enone | 1 | 97 | [26] |
| 17 | **1q** | *Ph*NH$_2$ | CH$_2$=CH–CN | 20 | 96 | [26] |
| 18 | **1r** | *Ph*NH$_2$ | CH$_2$=CH–COO*Me* | 20 | 95 | [26] |
| 19 | **1s** | 4-Cl*Ph*NH$_2$ | CH$_2$=CH–COO*Me* | 20 | 95 | [26] |
| 20 | **1t** | 4-*MePh*NH$_2$ | cyclohex-2-enone | 20 | 90 | [26] |
| 21 | **1u** | 4-(*MeO*)*Ph*NH$_2$ | | 20 | 98 | [26] |
| 22 | **1v** | Imidozole (*lm*) | CH$_2$=CH–CN | 20 | 98 | [25] |
| 23 | **1w** | 4-NO$_2$*lm* | CH$_2$=CH–COO*Me* | 30 | 96 | [25] |
| 24 | **1x** | 4-NO$_2$*lm* | CH$_2$=CH–CN | 30 | 95 | [25] |

[a] *BDO* 1,3-Benzodioxol-5-yl
[b] Isolated compounds
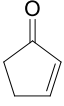
philicity of sulfur for addition to electron-deficient alkenes (Scheme 2).

The ionic liquid was recycled and reused for 10 times without apparent loss of reactivity and yield in the reaction of *N*-phenylpiperazine (**1c**) with acrylonitrile (Fig. 1). *TEAA* is air and water stable and easy to synthesize from triethylamine and acetic acid, which are relatively cheap. It is noteworthy that the preparation of *TEAA* ionic liquid is direct, simple, high yielding, and environment friendly, eliminating the need of volatile organic solvents, such as dichloromethane and acetonitrile used in some reported ionic liquids [22].

An experiment was performed for showing the chemoselectivity between thiols and aniline using acrylonitrile in *TEAA* (Scheme 3).

In the first condition, the *Michael* acceptor was used in 1.2 equivalents, whereas in second condition the *Michael* acceptor was used in 2.4 equivalents. The progress of reaction under both conditions was monitored after 1 min by TLC and GC analysis. The aniline remained unreacted while the thiol reacted completely with 100% conversion to the addition product **3**. After 20 min, the TLC and GC analysis found that both thiol and aniline were reacted completely to **3** and **4**. This experiment could be applied

**Table 2** Conjugate addition of aromatic thiols to conjugated alkenes

| Entry | Comp. | Enones | *R* | Time/min | Yield/%[a] | Ref. |
|---|---|---|---|---|---|---|
| 1 | **2a** | (cyclopentenone) | 4-*MePh*SH | 1 | 96 | [11] |
| 2 | **2b** | | *Ph*SH | 1 | 96 | [11] |
| 3 | **2c** | (cyclohexenone) | *Ph*CH$_2$SH | 1 | 99 | [11] |
| 4 | **2d** | | HS–(CH$_2$)$_7$CH$_3$ | 1 | 98[c] | |
| 5 | **2e** | | 4-NO$_2$*Ph*SH | 1 | 96 | [11] |
| 6 | **2f** | | 4-*MePh*SH | 1 | 99[c] | |
| 7 | **2g** | (methyl vinyl ketone) | *Ph*SH | 1 | 99 | [11] |
| 8 | **2h** | | 4-*MePh*SH | 1 | 99 | [11] |
| 9 | **2i** | (crotonaldehyde) | *Ph*SH | 1 | 95 | [7c] |
| 10 | **2j** | | 2-*MePh*SH | 1 | 97[c] | |
| 11 | **2k** | | 4-*MePh*SH | 1 | 96[c] | |
| 12 | **2l** | CN | HS–(CH$_2$)$_7$CH$_3$ | 1 | 99[c] | |

[a] Isolated yield
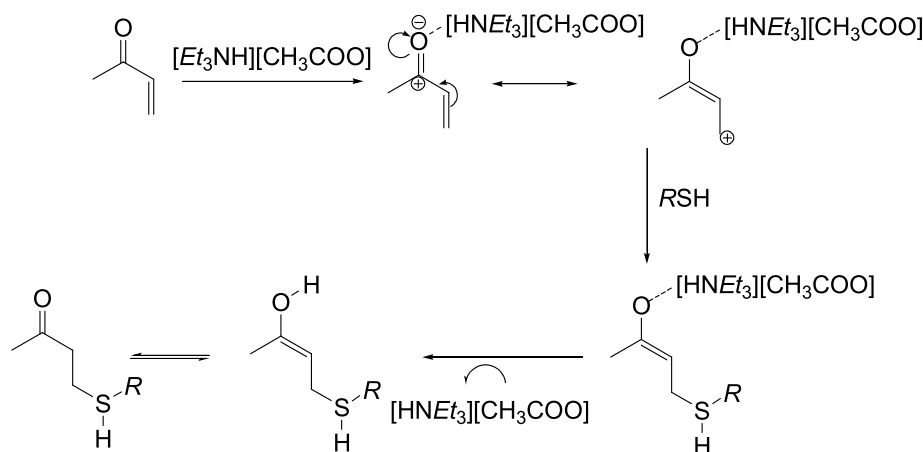


**Scheme 2**
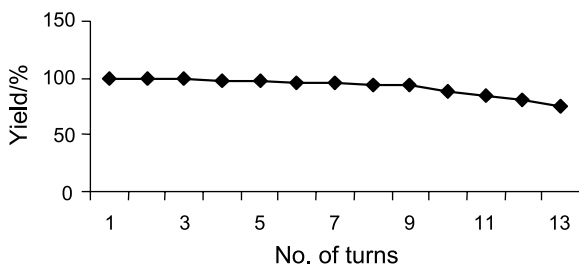


**Fig. 1** Catalytic cycles *versus* yield

in various synthesis applications. Thus, if we treat 1 mmol piperazine with 2.4 mmol acrylonitrile the di-alkyl addition product with addition of *TEAA* was obtained (Scheme 4).

This leads to the conclusion that if we take the *Michael* acceptor in about equimolar quantity it gave the mono-addition product (Table 1, **1a**), but if we take it in excess it will give the bis-addition product.

## Experimental

All reagents used were AR grade. Melting points were determined using a *Thomas Hoover* melting point apparatus and are corrected. ^{1}H (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded on a Bruker 300 NMR spectrometer in CDCl$_3$ (with *TMS* for ^{1}H and chloroform-*d* for ^{13}C as internal references) unless otherwise stated. Mass spectra were recorded on a Hybrid Quadrupole-TOF LC\MS\MS mass spectrometer (Q. Star XL). Microanalyses were obtained

**Scheme 3**



**Scheme 4**
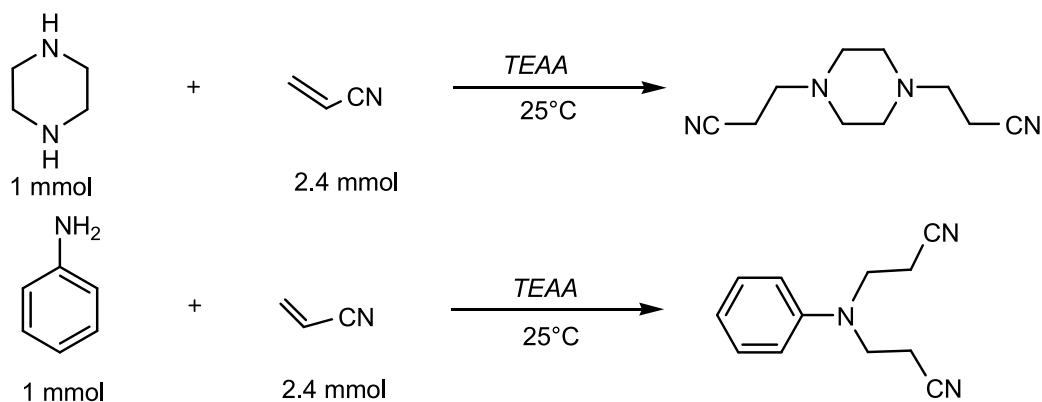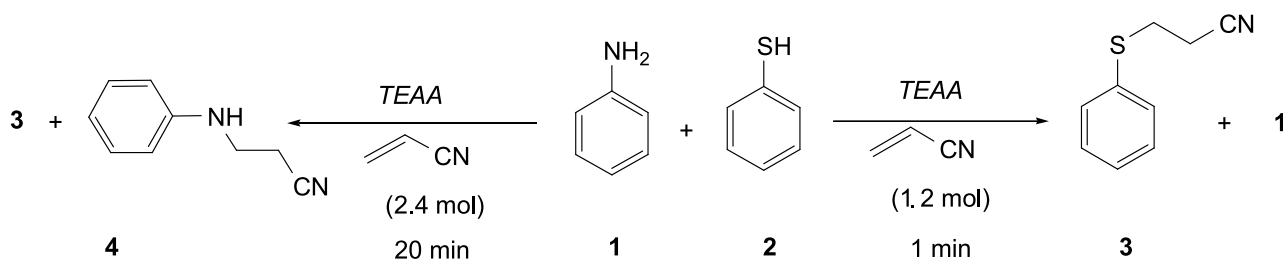
**Table 3** Comparison of different catalyst



| Entry | Catalyst | Time/h | Yield/% | Ref. |
|-------|----------|--------|---------|------|
| 1 | H$_2$O | 24 | 0 | [8] |
| 2 | [*bmim*][OH] | 84 | 96 | [18] |
| 3 | *CAN* | 24 | 78 | [9] |
| 4 | *β-CD* | 8 | 88 | [10] |
| 5 | solvent free | 24 | 2 | [13] |
| 6 | *TEAA* | 0.3 | 96 | |

with an Elemental Analysensysteme GmbH VarioEL V3.00 element analyzer. The results were in good agreement with the calculated values. The reactions were monitored by thin layer chromatography (TLC) using aluminum sheets with silica gel 60 F$_{254}$ (Merck).

*Modified procedure of triethylammonium ionic liquid (TEAA) synthesis* [23]

The synthesis of ionic liquid was carried out in a 250 cm$^3$ round-bottomed flask, which was immersed in a water-bath and fitted with a reflux condenser. Acetic acid (1.5 mol, 90.1 g, and 86.03 cm$^3$) was dropped into 101.2 g triethylamine (1 mol, 139.4 cm$^3$) at 70°C within 1 h. After the addition, the reaction mixture was stirred for 2 h at 80°C to ensure that the reaction had proceeded to completion. The reaction mixture was then dried at 80°C in high vacuum (5 mm Hg) until the weight of the residue remained constant. The yield of *TEAA* was 98%. $^1$H NMR (*DMSO-d$_6$*): $\delta = 1.18$ (t, 9H), 2.10 (s, 3H), 3.10 (m, 6H), 9.0 (s, 1H) ppm.

*Typical procedure for aza-Michael reaction of N-alkyl-, N-arylpiperazines, aromatic amines, and heterocycles with α,β-unsaturated nitriles and carbonyl compounds using TEAA ionic liquid*

A solution of 1 mmol amine and 1.2 mmol α,β-unsaturated nitriles and carbonyl compounds was added to 2 cm$^3$ *TEAA*,

and the mixture was stirred at 25°C for 1–30 min. The completion of the reactions was monitored by TLC. The product formed in the one-phase system, was extracted with $2 \times 25\,cm^3$ ether. The combined organic layer was separated, dried ($Na_2SO_4$), and evaporated under reduced pressure to afford the addition products. The aqueous layer consisting of the IL was subjected to distillation at 80°C and 5 mm Hg for 2 h to remove water, leaving behind the IL, which was further recycled. The conversion and the yield were not reduced after being reused 10 times. The products thus isolated, were pure and recrystallized from EtOAc:petroleum ether (single spot on TLC).

*General procedure of the thia-Michael reaction*

A solution of 1 mmol thiols and 1.2 mmol $\alpha,\beta$-unsaturated nitriles and carbonyl compounds in 2 $cm^3$ TEAA was stirred at 25°C for 1 min. The completions of the reactions were monitored by TLC. The product formed in one phase system was diluted with 20 $cm^3$ $H_2O$ and extracted with $2 \times 25\,cm^3$ ether. The combined organic layer was separated, dried ($Na_2SO_4$), and evaporated under reduced pressure to afford the addition products. The aqueous layer consisting of the IL was subjected to distillation at 80°C and 5 mmHg for 2 h to remove water, leaving behind the IL, which was further recycled. The conversion and the yield were not reduced after being reused 10 times. The products, thus isolated, were pure and recrystallized from EtOAc: petroleum ether (single spot on TLC).

*3-(4-Phenylpiperazin-1-yl)cyclohexanone* (**1e**, $C_{16}H_{22}N_2O$)
Colorless oil: $^1H$ NMR (300 MHz, $CDCl_3$): $\delta = 7.29$ (m, 2H), 7.92 (m, 3H), 3.20 (t, $J = 4.95$ Hz, 4H), 2.8–2.6 (m, 6H), 2.5–2.3 (m, 3H), 2.2–2.0 (m, 2H), 1.76–1.72 (m, 2H) ppm; $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta = 210.5$, 151.2, 129.1, 119.8, 116.1, 63.2, 49.5, 48.9, 44.4, 41.2, 28.1, 22.4 ppm; LC-MS: $m/z$ (%) = 258.17 (100, M + 1).

*3-[4-(4-Chlorophenyl)piperazin-1-yl]propionitrile*
(**1f**, $C_{13}H_{16}ClN_3$)
Light yellow solid, mp 98–100°C; $^1H$ NMR (300 MHz, $CDCl_3$): $\delta = 7.20$ (d, $J = 6.9$ Hz, 2H), 6.83 (d, $J = 6.9$ Hz, 2H), 3.17 (t, $J = 4.6$ Hz, 4H), 2.74 (t, $J = 6.9$ Hz, 2H), 2.66 (t, $J = 4.6$ Hz, 4H) 2.55 (t, $J = 6.8$ Hz, 2H) ppm; $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta = 149.6$, 128.9, 124.7, 118.5, 117.3, 52.5, 49.0, 15.9 ppm.

*3-[4-(4-Nitrophenyl)piperazin-1-yl]propionitrile*
(**1g**, $C_{13}H_{16}N_4O_2$)
Yellow solid, mp 92–94°C; $^1H$ NMR (300 MHz, $CDCl_3$): $\delta = 8.10$ (d, $J = 9.06$ Hz, 2H), 6.81 (d, $J = 9.12$ Hz, 2H), 3.44 (d, $J = 4.5$ Hz, 4H), 2.77–2.54 (m, 8H) ppm; $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta = 154.6$, 138.5, 125.8, 118.4, 112.7, 53.0, 52.0, 46.8, 16.0 ppm.

*3-[4-(4-Aminophenyl)piperazin-1-yl]propionitrile*
(**1h**, $C_{13}H_{18}N_4$)
Brown solid, mp 92–94°C; $^1H$ NMR (300 MHz, $CDCl_3$): $\delta = 6.80$ (d, $J = 8.2$ Hz, 2H), 6.64 (s, 8.3, 2H), 3.29 (s, br, 2H),

3.05 (t, $J = 4.6$ Hz, 4H), 2.76 (t, $J = 6.7$ Hz, 2H), 2.65 (t, $J = 4.5$ Hz, 4H), 2.56 (t, $J = 6.7$ Hz, 2H) ppm; $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta = 144.1$, 140.2, 118.6, 116.0, 53.2, 52.7, 50.7, 30.6, 15.7 ppm; LC-MS: $m/z$ (%) = 230.15 (100, M + 1).

*3-[4-[(Benzo[1,3]dioxol-5-yl)methyl]piperazin-1-yl]propionitrile* (**1i**, $C_{15}H_{19}N_3O_2$)
Mustard colour oil; $^1H$ NMR (300 MHz, $CDCl_3$): $\delta = 6.83$ (s, 1H), 6.73 (s, 2H), 5.93 (s, 2H), 3.40 (s, 2H), 2.68 (t, $J = 6.98$ Hz, 2H), 2.51–2.46 (m, 10H) ppm; $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta = 151.2$, 148.5, 138.0, 122.0, 109.3, 107.7, 100.7, 62.4, 53.1, 52.5, 31.7, 15. 6 ppm; LC-MS: $m/z$ (%) = 273.13 (100, M + 1).

*3-(Octylsulfanyl)cyclohexanone* (**2d**, $C_{14}H_{26}OS$)
Colorless oil; $^1H$ NMR (300 MHz, $CDCl_3$): $\delta = 0.89$ (t, $J = 6.6$ Hz, 3H), 1.26–1.36 (m, 10H), 1.51–1.59 (m, 2H), 1.66–1.75 (m, 2H), 2.11–2.17 (m, 2H), 2.33–2.35 (m, 4H), 2.52 (t, $J = 7.35$ Hz, 2H), 3.05–3.57 (m, 1H) ppm; $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta = 14.06$, 22.61, 24.26, 25.65, 28.93, 29.14, 29.69, 30.53, 31.65, 31.76, 40.95, 42.74, 48.25, 209.02 ppm; LC-MS : $m/z$ (%) = 242.17 (100, M + 1).

*3-(p-Tolylsulfanyl)cyclohexanone* (**2f**, $C_{13}H_{16}OS$)
Colorless oil; $^1H$ NMR (300 MHz, $CDCl_3$): $\delta = 1.61$–1.77 (m, 2H), 2.01–2.69 (m, 9H), 2.63–3.36 (m, 1H), 7.09–7.14 (m, 2H), 7.32–7.39 (m, 2H) ppm; $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta = 21.1$, 24.1, 31.3, 40.8, 46.5, 47.8, 128.5, 129.1, 129.8, 133.9, 138.2, 208.9 ppm; LC-MS: $m/z$ (%) = 220.1 (100, M + 1).

*3-(2-Methoxyphenylsulfanyl)butyraldehyde* (**2j**, $C_{11}H_{14}O_2S$)
Colorless oil; $^1H$ NMR (300 MHz, $CDCl_3$): $\delta = 2.52$–2.72 (m, 3H), 3.89 (s, 3H), 6.82–6.95 (m, 3H), 7.24–7.34 (m, 1H) ppm; $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta = 21.0$, 35.8, 50.2, 55.7, 110.9, 121.0, 121.3, 127.6, 129.4, 159.1, 200.9 ppm; LC-MS: $m/z$ (%) = 210.1 (100, M + 1).

*3-p-Tolylsulfanyl-butyraldehyde* (**2k**, $C_{11}H_{14}OS$)
Colorless oil; $^1H$ NMR (300 MHz, $CDCl_3$): $\delta = 1.35$–1.37 (d, $J = 6.90$ Hz, 3H), 2.42 (s, 3H), 2.56–2.75 (m, 2H), 3.64–3.75 (m, 1H), 7.12–7.41 (m, 4H), 9.75 (s, 1H) ppm; $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta = 20.8$, 21.0, 36.9, 50.2, 126.5, 126.7, 127.5, 130.5, 132.6, 133.3, 140.2, 200.4 ppm; LC-MS: $m/z$ (%) = 194.0 (100, M + 1).

*3-(Octylsulfanyl)propionitrile* (**2l**, $C_{11}H_{21}NS$)
Colorless oil; $^1H$ NMR (300 MHz, $CDCl_3$): $\delta = 0.88$ (t, $J = 6.0$ Hz, 3H), 1.27–1.40 (m, 10H), 1.54–1.69 (m, 2H), 2.56–2.66 (m, 4H), 2.75–2.80 (m, 2H) ppm; $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta = 14.09$, 18.93, 22.42, 22.64, 27.40, 28.55, 29.24, 29.94, 31.81, 32.04, 118.24 ppm; LC-MS: $m/z$ (%) = 199.14 (100, M + 1).

## Acknowledgements

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