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# Multicomponent reactions in fungicide research: The discovery of mandipropamid

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**Abstract**—Isocyanide-based multicomponent reactions of the Ugi- and Passerini-type have been valuable tools for the rapid exploration of the novel fungicidal compound classes of phenylglycinamides and mandelamides. Mandipropamid (**6**), which was discovered during this derivatisation, displays excellent activity against the economically important phytopathogens *Phytophthora infestans* (potato and tomato late blight) and *Plasmopara viticola* (grape downy mildew).


## 1. Introduction

In the meantime multicomponent reactions are well-established as a powerful tool for the rapid construction of complex and structurally diverse compounds from relatively simple building blocks.[1] High atom-economy, chemical efficiency and convergence are typical features of such one-pot condensations of at least three different starting materials. Because of the remarkable high purity of libraries, multicomponent reactions are well-suited for both combinatorial chemistry and high-speed parallel synthesis and therefore possess high exploratory power.[2] Especially isocyanide-based[3] and asymmetric[4] multicomponent reactions have been emerging fields of interest in the last decade, but the construction of heterocycles via multicomponent reactions was also in the focus recently.[5] However, there are only a few applications of multicomponent reactions in fungicide research so far.[6,7] In our Laboratorys, isocyanide-based multicomponent reactions of the Ugi- and Passerini-type have just recently been key instruments for the rapid exploration of the novel fungicide compound classes of phenylglycinamides[8] and mandelamides.[9,10] Herein we report how such reactions contributed significantly to the discovery of the novel oomycetes fungicide mandipropamid (**6**).

The oomycetes are a family of more than 800 different species, which are more related to algae than to fungi.[11] Some of them live in aquatic, others in terrestrial biotopes, some are saprophytes (feeding on dead material), others are parasites. Despite this ecological diversity, the oomycetes are a well-defined unit of high physiological and biochemical uniformity. Their cell walls consist mainly of cellulose, glucans and hydroxyproline instead of chitin, which is common in most other phytopathogenic fungi, such as the ascomycetes, the basidiomycetes and the deuteromycetes. In addition, the life cycle of oomycetes is primarily diploid and not haploid as in higher fungi. Parasitic members of the oomycetes family are for instance *Peronospara tabacina* (tobacco blue mold) and *Pythium ultimum* (damping-off), but the economically most important diseases are *Plasmopara viticola* (grape downy mildew) and *Phytophthora infestans* (potato and tomato late blight). The latter pathogen caused the complete devastation of the Irish potato crop between the years 1845 and 1849. The dependence of the rural population on the potato harvest and the non-existence of chemical crop protection resulted in a famine of unbelievable dimensions, during which one million Irish people starved to death and two millions emigrated to North America.[12] In the meantime there are several

*Keywords*: Fungicide; Crop protection; Multicomponent reaction; Ugi reaction; Passerini reaction; Isocyanide; Oomycetes diseases; *Phytophthora infestans*; *Plasmopara viticola*.
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well-established oomycetes fungicides on the market. However, the pressure especially on older products because of increased resistance, expired patent protection and public discussions around regular re-registrations stimulates the search for new agrochemicals with high activity and a favourable environmental profile.

In the mid 1990s we were intrigued by the valinamide **1**, which was patented by American Cyanamid (now BASF) as a compound with anti-oomycetic activity (Fig. 1).[13] Because of in-house experience with sulfonylated amino acids, we decided to start a derivatisation of that lead structure. The replacement of the carbamate function by a sulfonamide and the elongation of one of the methoxy groups to a 4-chlorophenylpropargyloxy substituent finally led to the valinamide **2** with improved fungicidal activity.[8] During the optimisation of **2**, we found out that the isopropyl group of the valinamides could be replaced by substituted phenyl rings with excellent biological results. Best fungicidal activity of such novel phenylglycinamides was achieved, when their 4-chlorophenylpropargyloxy function was shortened to a simple propargyloxy group, as in **3**. Approximately at the same time we realised that Agrevo (now Bayer) had found quite similar mandelamides, such as **4**, which were unfortunately only weakly active against oomycetes diseases.[7,14] Convinced that the propargyloxy group in our phenylglycinamide **3** was responsible for at least part of its excellent fungicidal efficacy, we applied the propargylation also to the field of mandelamides. Actually, the resulting compound **5** was clearly more active than the non-propargylated lead compound **4**. The replacement of methoxy or ethoxy groups by a propargyloxy has also been reported in the pharmaceutical literature for compounds with antibacterial[15] and leishmanicidal[16] activity to lead to increased biological activity. During the further optimisation of the mandelamide **5**, the simplest manipulation was the most successful. The introduction of a further propargyl group into the mandelic acid moiety of the molecule resulted in the discovery of mandipropamid (**6**), which is highly active against most foliar oomycete pathogens such as the economically important diseases *P. infestans* (potato and tomato late blight), *P. viticola* (grape downy mildew) and *Pseudoperonospara cubensis* (cucumber downy mildew). Mandipropamid is highly effective in preventing spore germination, but also inhibits mycelial growth and sporulation.[17] Being rapidly adsorbed to the wax layer of the plant surface,[18] mandipropamid provides a rainfast and long-lasting barrier to fungal diseases. It will be launched to the agrochemical market in 2007 under the trade names Revus© and Pergado©.

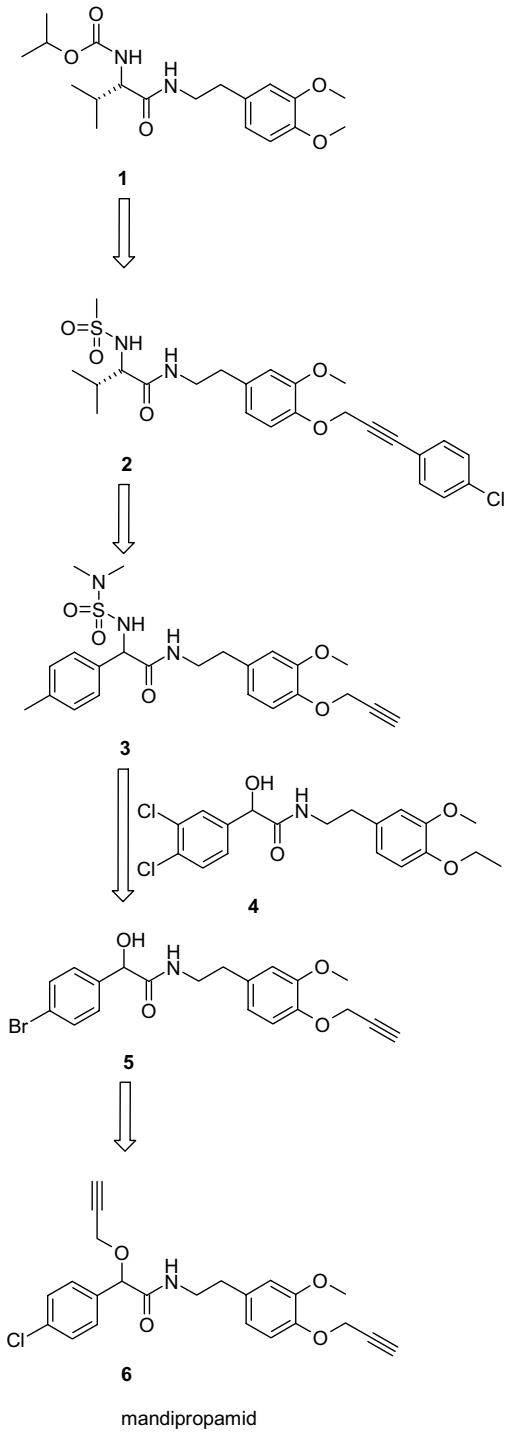



**Figure 1.** Invention pathway from valinamide **1** to mandipropamid (**6**).

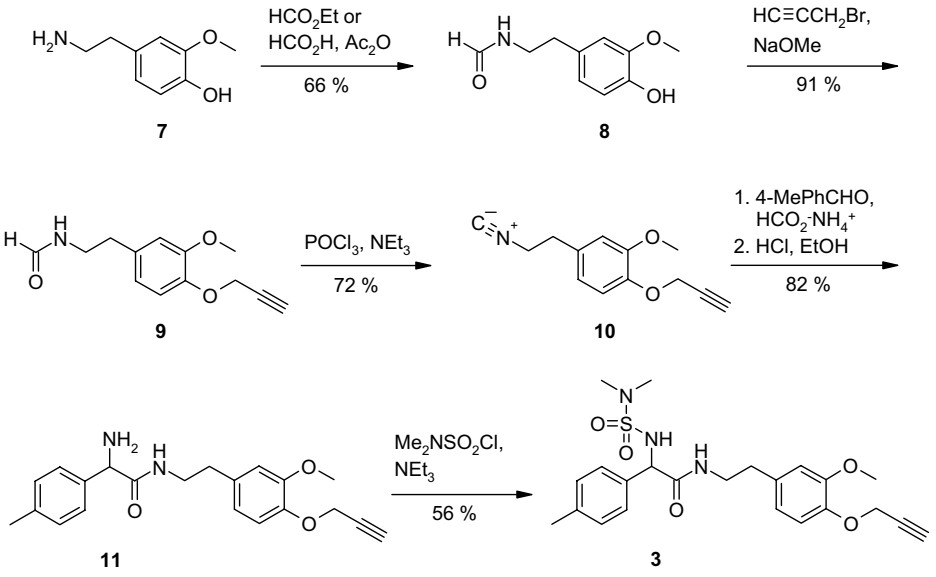
## 2. Chemistry

The phenylglycinamides seemed to be predestined to be prepared by an Ugi four component condensation,[3] because this reaction offers huge flexibility in the introduction of substituents into the phenyl ring of the acid moiety. This was important for the optimisation of this subclass, because from the first assays it was clear that at this position we had the broadest chemical scope. The Ugi reaction is a classical multicomponent condensation, in which an amine, a carbonyl compound, a carboxylic acid and an isocyanide are assembled in one step to an α-acylaminocarboxamide, a new stereogenic centre is formed at the carbon atom derived from the prochiral carbonyl group. Therefore, the phenethylamine **7**, which is available in two steps from vanilline,[8] was converted into the stable and odourless isocyanide **10** by standard N-formylation, O-propargylation and dehydration. Hereby, the formyl group serves as

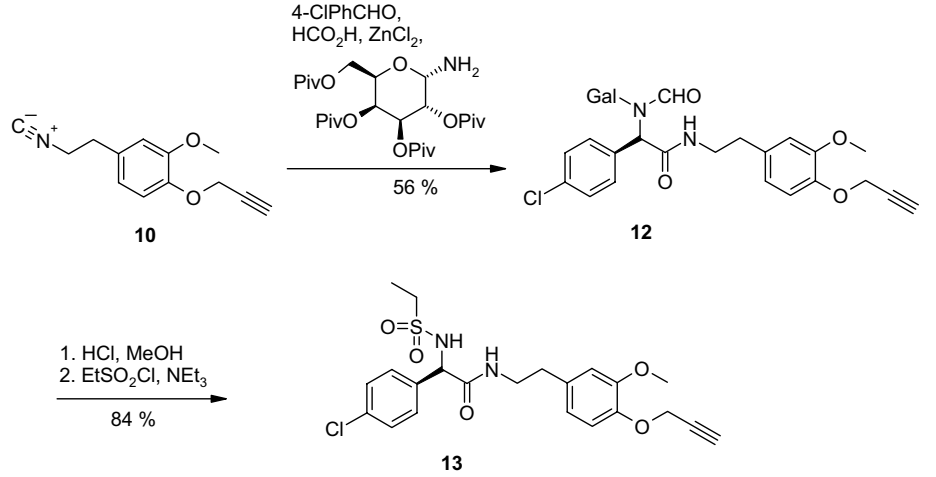
protecting group for the amine function during the alkylation of the phenol and also as precursor for the formation of the isocyanide function. The Ugi reaction of the isocyanide **10** with *p*-tolualdehyde and ammonium formate, which is both the acid and the amine component, led to a *N*-formylphenylglycinamide, which could be transformed into the phenylglycinamide **11** with a free amino group by acidic hydrolysis. Finally, N-sulfonylation of **11** yielded the desired *N*-sulfonylphenylglycinamide **3**[8] (Scheme 1).

Enantiomerically pure phenylglycinamides could be obtained by carrying out the Ugi reaction with a chiral amine.[19] The condensation of isocyanide **10** with 4-chlorobenzaldehyde, formic acid and 2,3,4,6-tetra-*O*-pivaloylgalactosamine resulted in the diastereoselective formation of the intermediate **12**. Removal of the sugar unit, which served as chiral inducer during the transformation, as well as of the formyl group and subsequent sulfonylation delivered the fungicidally active (*R*)-phenylglycinamide **13** (Scheme 2). In a similar manner, we have developed a novel asymmetric synthesis of enantiopure mandelamide fungicides via a diastereoselective Passerini reaction with a galacturonic acid derivative as the acid component[20].

The formamide **9**, which was already a key intermediate during the Ugi synthesis of phenylglycinamides, proved to be also of high value for the preparation of mandelamides. Building block **9** could be directly transformed by Seebach's variation[21] of the Passerini reaction[3] into the mandelamide **14**. In the classical Passerini reaction, an isocyanide is condensed with an aldehyde and a carboxylic acid to afford α-acyloxycarboxamides. During the reaction, a C–C bond is formed between the carbonyl carbon atom and the isocyano carbon atom. Using Seebach's variation, the application of Lewis acids, like titanium(IV) chloride, instead of carboxylic acids as acid component delivers not the common α-acyloxycarboxamides, but directly α-hydroxycarboxamides.[21] Similar




**Scheme 1.** Synthesis of the phenylglycinamide fungicide **3** via the Ugi product **11**.



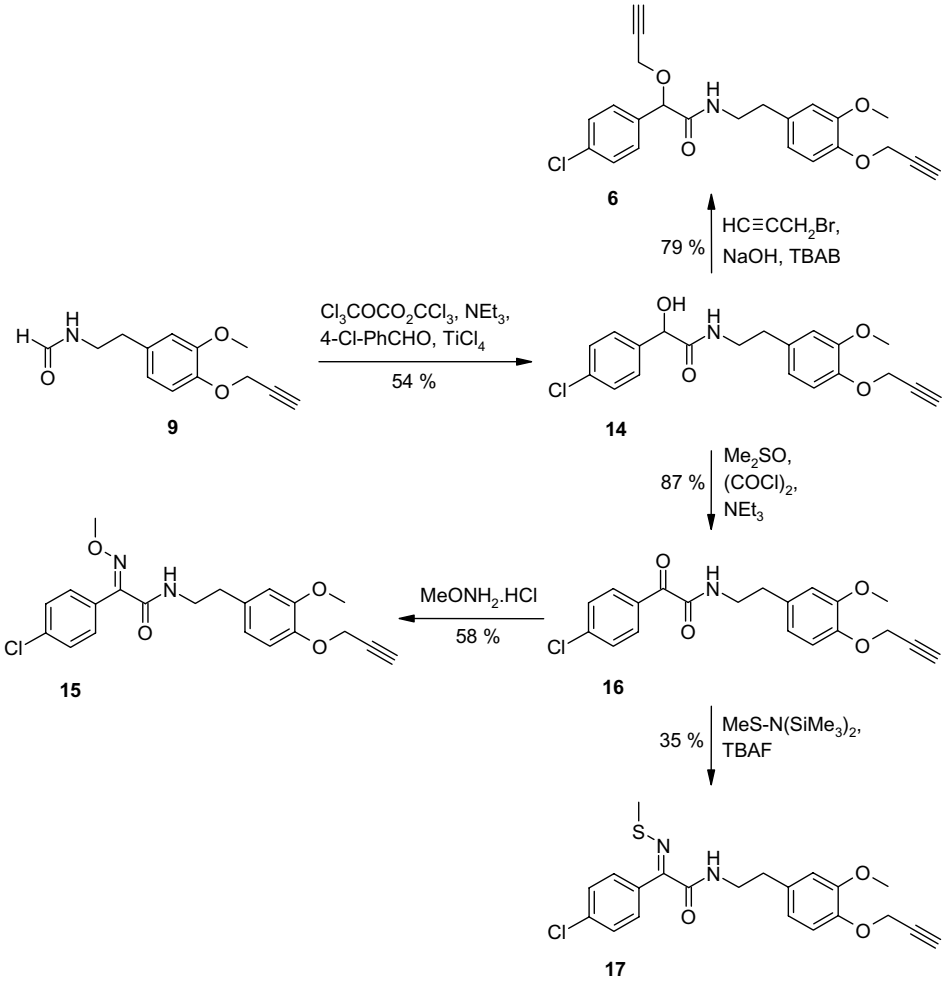

**Scheme 2.** Diastereoselective synthesis of the phenylglycinamide fungicide **13**.

Passerini-type transformations leading directly to α-hydroxycarboxamides have also been reported with trifluoroacetic acid,[22] boron trifluoride,[23,24] mineral acids[24,25] and even water[26] as acid component. The introduction of a second propargyl group into the hydroxy group of the mandelic acid moiety of **14** delivers mandipropamid (**6**).[9] The mandelamide **14** could also be easily converted into the phenylglyoxylic acid amide **16**[27] via Swern oxidation. This versatile building block opened the road to two further fungicide classes, in which the keto function of **16** is transformed into either an *O*-methyloxime, as in **15**,[27,28] or a methylsulfenimine, as in **17**.[29] The synthesis of the latter subclass succeeded according to Morimoto's unique one-step procedure with *N*,*N*-bis(trimethylsilyl)methanesulfenamide[30] (Scheme 3).

## 3. Results and discussion

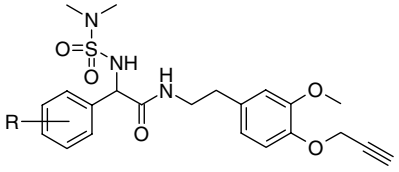
To determine the efficacy of the new phenylglycinamides and mandelamides against *P. infestans* and *P. viticola*, three-week-old tomato plants and five-week-old grape seedlings were treated with the test compounds in a spray chamber. One day (grape) or two days (tomato) after application, the plants were inoculated by spraying a sporangial suspension on the upper (tomato) or lower (grape) side of the leaves. Disease incidence was assessed after an incubation period of 4 days (tomato) or 6 days (grape) at 20 °C and 95% relative humidity in a greenhouse.

Table 1 presents several phenylglycinamides, bearing different substituents in the phenyl ring of the amino acid moiety, together with their $EC_{80}$ values, which are the concentrations in mg $L^{-1}$ (equivalent to ppm) obtained from greenhouse trials where the tested compound shows 80% activity. Quite soon it became obvious that small alkyl groups in the *para*-position, like in **3** and **25**, will achieve the best results. Also the *para*-trifluoromethylated derivative **24** possesses interesting fungicidal activity. Compound **19**, the *ortho*-substituted regioisomer of **3**, is completely inactive, whereas the *meta*-substituted analogue **20** displays only weak efficacy. Halogen or alkoxy substituents in position 4 seem to be less advantageous. Very interesting is the influence of the alkyl chain branching factor on the activity against *P. infestans*. Linear alkyl groups, like ethyl in **25** and *n*-propyl in **27**, lead to a much better efficacy than branched alkyl groups, like *iso*-propyl in **26** and




**Scheme 3.** Synthesis of the mandelamide fungicide mandipropamid (**6**) and the phenylglyoxylic acid amide fungicides **15** and **17** via the Passerini product **14**.

**Table 1.** $EC_{80}$ values of different phenylglycinamides against *Phytophthora infestans* and *Plasmopara viticola*

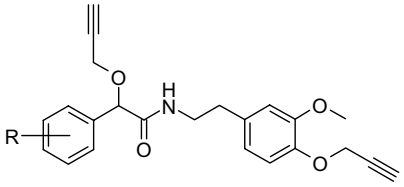


| Compound | R | $EC_{80}$ (mg $L^{-1}$) | |
|---|---|---|---|
| | | *Phytophthora infestans* (tomato late blight) | *Plasmopara viticola* (grape downy mildew) |
| **18** | H | 81.2 | 28.5 |
| **19** | 2-$CH_3$ | >200 | >200 |
| **20** | 3-$CH_3$ | 149.9 | 116.1 |
| **21** | 4-F | 45.7 | 78.3 |
| **22** | 4-Cl | 10.6 | 13.8 |
| **23** | 4-Br | 7.8 | 39.4 |
| **3** | 4-$CH_3$ | 2.5 | 3.2 |
| **24** | 4-$CF_3$ | 3.4 | 5.8 |
| **25** | 4-$CH_2CH_3$ | 2.6 | 5.1 |
| **26** | 4-$CH(CH_3)_2$ | 26.2 | 14.6 |
| **27** | 4-$CH_2CH_2CH_3$ | 3.1 | 16.7 |
| **28** | 4-$C(CH_3)_3$ | 142.8 | 20.2 |
| **29** | 4-$OCH_3$ | 8.0 | 34.9 |
| **30** | 4-$OCF_3$ | 18.8 | 46.4 |
| **31** | 4-$OCH_2CH_3$ | 24.7 | 35.0 |
| **32** | 4-$SCH_3$ | 34.9 | 16.2 |
| **33** | 3-Cl–4-Cl | 19.2 | 51.5 |
| **34** | 3-Cl–4-F | 186.0 | 59.8 |
| **35** | 3-F–4-F | 109.6 | 46.3 |
| **36** | 3-$CH_3$–4-$CH_3$ | 12.2 | 28.7 |

*tert*-butyl in **28**. A comparison between the 3,4-disubstituted compounds **33** and **36** and their monosubstituted counterparts **22** and **3** demonstrates that the introduction of an additional group into the *meta*-position is not advantageous. The influence of different sulfonyl groups on the fungicidal activity of phenylglycinamides has already been described.[8]

Mandelamides possess a much higher level of antioomycetic potency than phenylglycinamides, as manifested in Table 2. Regarding structure–activity relationship, both subclasses possess many similarities. As it has been already the case for phenylglycinamides, the introduction of small lipophilic groups into the *para*-position of the phenyl ring of the acid moiety is also for mandelamides a requirement for best biological results. In contrast to the small alkyl groups, which achieved the highest activity in the phenylglycinamide family, halogens are the optimum as *para*-substituents in the mandelic acid moiety of mandelamides (e.g., **6**, **45**, **46**). However, surprisingly the unsubstituted mandelamide **37** was the second most active derivative behind the *para*-chlorosubstituted mandipropamid (**6**), which showed outstanding control of both plant diseases. *Meta*-substituted mandelamides, such as **40**, **41** and **42**, are still quite active, but clearly weaker than their *para*-substituted counterparts. *Ortho*-substituents other than hydrogen have a negative effect on the fungicidal

**Table 2.** $EC_{80}$ values of different mandelamides against *Phytophthora infestans* and *Plasmopara viticola*

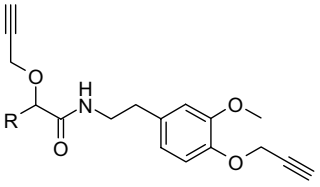


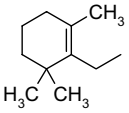
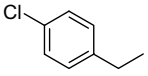
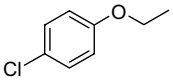
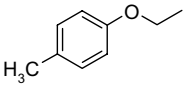
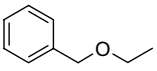
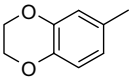
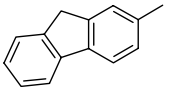
| Compound | R | $EC_{80}$ (mg $L^{-1}$) | |
|---|---|---|---|
| | | *Phytophthora infestans* (tomato late blight) | *Plasmopara viticola* (grape downy mildew) |
| **37** | H | 0.5 | 1.3 |
| **38** | 2-Cl | 81.1 | >200 |
| **39** | 3-F | 10.2 | 1.8 |
| **40** | 3-Cl | 3.7 | 2.4 |
| **41** | 3-Br | 4.9 | 4.9 |
| **42** | 3-$CH_3$ | 6.4 | 1.7 |
| **43** | 3-$CF_3$ | 5.0 | 3.8 |
| **44** | 3-$OCH_3$ | 46.2 | 1.7 |
| **45** | 4-F | 1.8 | 3.4 |
| **6** | 4-Cl | 0.1 | 1.2 |
| **46** | 4-Br | 3.4 | 2.6 |
| **47** | 4-$CH_3$ | 9.7 | 5.2 |
| **48** | 4-$CF_3$ | 8.0 | 11.6 |
| **49** | 4-$CH_2OCH_3$ | 2.6 | 13.8 |
| **50** | 4-$CH_2CH_3$ | 7.5 | 3.1 |
| **51** | 4-$CH{=}CH_2$ | 3.3 | 2.0 |
| **52** | 4-$CH_2CH_2CH_3$ | 4.4 | 1.7 |
| **53** | 4-$CH(CH_3)_2$ | 6.1 | 2.8 |
| **54** | 4-$CH_2CH_2CH_2CH_3$ | 25.9 | 10.4 |
| **55** | 4-$OCH_3$ | 2.3 | 1.6 |
| **56** | 4-$SCH_3$ | 7.6 | 5.3 |
| **57** | 2-Cl–3-Cl | 168.4 | 25.5 |
| **58** | 3-Cl–4-Cl | 4.8 | 3.4 |
| **59** | 2-F–4-F | 4.6 | 5.0 |
| **60** | 2-F–4-Br | 5.3 | 1.8 |
| **61** | 3-Cl–4-$CH_3$ | 2.4 | 1.5 |
| **62** | 3-$CH_3$–4-$CH_3$ | 3.2 | 1.6 |
| **63** | 3-$CH_3$–5-$CH_3$ | 41.9 | 56.4 |
| **64** | 3-F–4-F–5-F | 26.2 | 19.7 |
| **65** | 2-Cl–3-Cl–5-Cl | >200 | 44.2 |

efficacy, as in **38** and **57**, with fluorine as the only exception (**59** and **60**). If the phenyl ring bears two substituents, then 3,4-disubstituted mandelamides such as **58** and **62** show much better activity than the corresponding 2,4- or 3,5-disubstituted compounds such as **57** and **63**. Also trisubstituted mandelamides such as **64** and **65** have been prepared, but do not belong to the most active compounds. The influence of other substituents than propargyl in the mandelic acid moiety as well as in the phenethylamine part of mandipropamid on the fungicidal activity of mandelamides has already been described.[9]

The huge importance of the Passerini reaction in the derivatisation of mandipropamid is demonstrated in Table 3. A broad variety of aliphatic, aromatic and heterocyclic as well as mono-, bi- and tricyclic aldehydes could easily be converted to the corresponding α-propargyloxyacetamides. Especially noteworthy is the

**Table 3.** $EC_{80}$ values of different α-propargyloxyacetamides against *Phytophthora infestans* and *Plasmopara viticola*



| Compound | R | $EC_{80}$ (mg $L^{-1}$) | |
|---|---|---|---|
| | | *Phytophthora infestans* (tomato late blight) | *Plasmopara viticola* (grape downy mildew) |
| **66** |  | 47.6 | 5.3 |
| **67** |  | 51.4 | 124.0 |
| **68** |  | 26.3 | 18.6 |
| **69** |  | 0.02 | 0.6 |
| **70** |  | 0.1 | 1.8 |
| **71** |  | 0.3 | 20.4 |
| **72** |  | 16.7 | 2.2 |
| **73** |  | 4.8 | 19.3 |
| **74** |  | 2.1 | 1.4 |
| **75** |  | 186.3 | >200 |

'stretched' mandelamide **69**, whose impressive efficacy against *P. infestans* down to 0.02 mg $L^{-1}$ was unrivalled by all other mandelamide derivatives. This compound, which bears an $OCH_2$ linker between the 4-chlorophenyl ring and the 2-propargyloxyacetamide function of mandipropamid, could be obtained by Passerini reaction from (4-chlorophenoxy)acetaldehyde.[31] Interestingly, stretched mandelamides with one-atom O or $CH_2$ spacers, as in **68**, possess a much weaker activity. The 4-chlorophenyl ring of mandipropamid can be replaced by heterocycles with very good biological results, as demonstrated by the thiophene derivative **74**.[31] However, heterocyclic six-membered ring mandipropamid analogs, such as the pyridine **75**, did not show sufficient fungicidal activity.

## 4. Conclusion

Many phenylglycinamides and mandelamides with a different substitution pattern in the phenyl ring of the acid moiety possess high fungicidal activity against the oomycetes diseases *P. infestans* and *P. viticola*. The structure–activity relationship of these chemical classes could be explored very rapidly by direct conversion of commercially available benzaldehydes into phenylglycinamides and mandelamides under the conditions of the Ugi and Passerini reactions. Hereby, the lengthy construction of the corresponding phenylglycines and mandelic acids and their subsequent transformation into amides could be avoided. Mandipropamid (**6**), a novel fungicide with powerful performance against major oomycetes diseases, was discovered during this optimisation.

## 5. Experimental

All new compounds were characterised by standard spectroscopical and microanalytical methods. $^1H$ and $^{13}C$ NMR spectra were recorded on a Varian Unity 400 spectrometer at 400 and 100 MHz, using $CDCl_3$ or $(CD_3)_2SO$ as solvents and tetramethylsilane as internal standard. Chemical shifts are reported in ppm downfield from the standard ($\delta = 0.00$). Mass spectra were obtained on Micromass LCT and Finnigan MAT mass spectrometers. Melting points were determined on a Büchi 535 melting point apparatus and are uncorrected. Analytical thin-layer chromatography (TLC) was performed using silica gel 60 F524 precoated plates. Preparative flash chromatography was performed using silica gel 60 (40–63 μm, E. Merck). All reactions were carried out under anhydrous conditions in an inert atmosphere (nitrogen or argon) with dry solvents.

### 5.1. *N*-[2-(4-Hydroxy-3-methoxyphenyl)-ethyl]-formamide (8)

Formic acid (230 g, 5.0 mol) was added dropwise to acetic anhydride (383 g, 3.75 mol) at 0 °C. This mixture was stirred for 2 h at 55 °C and subsequently cooled again to 0 °C. Five hundred microlitres of tetrahydrofuran was then added, followed by 4-(2-aminoethyl)-2-methoxyphenol hydrochloride (**7**, 50 g, 0.25 mol).[8] The resulting white suspension was stirred for 16 h at 75 °C while it changed into a yellow solution. The reaction mixture was evaporated and the residue was purified by chroma-

tography on silica gel (ethyl acetate/hexane, 1:3). Yield: 32 g (0.16 mol, 66%). $^1$H NMR ($CDCl_3$): $\delta$ 2.85 (t, 2H, $CH_2CH_2$), 3.57 (t, 2H, $CH_2CH_2$), 3.82 (s, 3H, $OCH_3$), 5.69 (br s, 1H, NH), 6.67–7.09 (m, 3H, CH arom.), 8.12 (s, 1H, CHO). $^{13}$C NMR ($CDCl_3$): $\delta$ 35.1, 45.9, 55.9, 111.5, 114.7, 121.3, 130.3, 144.4, 146.8, 161.5. HRMS *m/z*: Calcd for $(C_{10}H_{13}NO_3+H)^+$: 196.0968. Found: 196.0966.

### 5.2. *N*-[2-(3-Methoxy-4-prop-2-ynyloxyphenyl)-ethyl]-formamide (9)

Sodium methoxide (32 ml of a 5.4 M solution in methanol, 0.17 mol) was added to a solution of *N*-[2-(4-hydroxy-3-methoxyphenyl)-ethyl]-formamide (**8**, 32 g, 0.16 mol) in 400 ml of methanol. Propargyl bromide (20 g, 0.17 mol) was added and the mixture was refluxed for 4 h. The reaction mixture was evaporated and the residue was taken up in ethyl acetate and washed twice with water. The organic layer was dried over magnesium sulfate and evaporated. The remainder was purified by chromatography on silica gel (ethyl acetate/hexane, 1:4). Yield: 34 g (0.14 mol, 91%). $^1$H NMR ($CDCl_3$): $\delta$ 2.44 (t, 1H, C≡CH), 2.73 (t, 2H, $CH_2CH_2$), 3.51 (t, 2H, $CH_2CH_2$), 3.82 (s, 3H, $OCH_3$), 4.69 (m, 2H, $CH_2C{\equiv}C$), 5.53 (br s, 1H, NH), 6.62–6.95 (m, 3H, CH arom.), 8.09 (s, 1H, CHO). $^{13}$C NMR ($CDCl_3$): $\delta$ 35.1, 39.2, 55.9, 56.9, 75.8, 78.6, 112.4, 114.7, 120.6, 132.7, 145.5, 149.8, 161.3. HRMS *m/z*: Calcd for $(C_{13}H_{15}NO_3+H)^+$: 234.1125. Found: 234.1125.

### 5.3. 4-(2-Isocyanoethyl)-2-methoxy-1-prop-2-ynyloxy-benzene (10)

Triethylamine (20 g, 0.2 mol) was added to a solution of *N*-[2-(3-methoxy-4-prop-2-ynyloxyphenyl)-ethyl]-formamide (**9**, 8.5 g, 40 mmol) in 65 ml of tetrahydrofuran and the mixture was cooled to −10 °C. A solution of phosphorus oxychloride (6.6 g, 43 mmol) in 20 ml of tetrahydrofuran was added dropwise at this temperature, maintaining the reaction temperature during the addition between −10 and 0 °C. Subsequently the reaction mixture was stirred at 0 °C for 2 h, cooled down to −20 °C and quenched by addition of 80 ml of water. The mixture was extracted twice with *tert*-butyl methyl ether. The combined organic phases were dried over magnesium sulfate and evaporated. The remainder was crystallised from ethyl acetate/hexane 1:1. Yield: 6.2 g (29 mmol, 72%). $^1$H NMR ($CDCl_3$): $\delta$ 2.52 (t, 1H, C≡CH), 2.94 (t, 2H, $CH_2CH_2$), 3.59 (t, 2H, $CH_2CH_2$), 3.85 (s, 3H, $OCH_3$), 4.73 (d, 2H, $CH_2C{\equiv}C$), 6.76–7.01 (m, 3H, CH arom.). $^{13}$C NMR ($CDCl_3$): $\delta$ 35.2, 43.1, 55.9, 56.8, 75.8, 78.6, 112.5, 114.7, 120.6, 130.8, 146.0, 149.8, 156.7. HRMS *m/z*: Calcd for $(C_{13}H_{13}NO_2+H)^+$: 216.1019. Found: 216.1022.

### 5.4. 2-Amino-*N*-[2-(3-methoxy-4-prop-2-ynyloxyphenyl)-ethyl]-2-*p*-tolylacetamide (11)

A mixture of 4-(2-isocyanoethyl)-2-methoxy-1-prop-2-ynyloxybenzene (**10**, 5.0 g, 23 mmol), *p*-tolualdehyde (3.4 g, 28 mmol) and ammonium formate (2.9 g, 46 mmol) in 30 ml of methanol was heated to reflux for 6 h. The reaction mixture was cooled to 0 °C and 10 ml of a 10 M solution of hydrogen chloride in methanol was added. The reaction mixture was stirred at room temperature for 16 h. The mixture was then poured on ice-water and washed with ethyl acetate. The aqueous phase was made basic by the addition of 1 N sodium hydroxide and then extracted twice with ethyl acetate. The combined organic layers were dried over magnesium sulfate and evaporated, the remainder was used in the next step without any further purification. Yield: 6.7 g (19 mol, 82%). $^1$H NMR ($CDCl_3$): $\delta$ 2.38 (s, 3H, $CH_3$), 2.51 (t, 1H, C≡CH), 2.76 (t, 2H, $CH_2CH_2$), 3.52 (q, 2H, $CH_2CH_2$), 3.83 (s, 3H, $OCH_3$), 4.48 (s, 1H, CHN), 4.73 (d, 2H, $CH_2C{\equiv}C$), 6.62–7.24 (m, 7H, CH arom.). $^{13}$C NMR ($CDCl_3$): $\delta$ 21.1, 34.6, 41.1, 55.7, 56.7, 56.9, 74.3, 75.7, 78.7, 112.5, 114.7, 120.4, 127.7, 129.6, 129.9, 132.5, 139.9, 141.0, 145.4, 149.6, 168.1. HRMS *m/z*: Calcd for $(C_{21}H_{24}N_2O_3+H)^+$: 353.1860. Found: 353.1863.

#### 5.4.1. 2-[(*N*,*N*′-Dimethylamino)-sulfonylamino]-*N*-[2-(3-methoxy-4-prop-2-ynyloxy-phenyl)-ethyl]-2-*p*-tolyl-acetamide (3).

2-Amino-*N*-[2-(3-methoxy-4-prop-2-ynyloxy-phenyl)-ethyl]-2-*p*-tolylacetamide (**11**, 2.6 g, 7.5 mmol) was dissolved in 25 ml of tetrahydrofuran and cooled to 0 °C. *N*,*N*-Dimethylsulfamoyl chloride (1.6 g, 11 mmol) and triethylamine (3.1 g, 31 mmol) were added and the mixture was stirred for 16 h at room temperature. Subsequently the reaction mixture was taken up in ethyl acetate and washed with water. The combined organic layer was dried over magnesium sulfate and evaporated, the residue was purified by silica gel chromatography (ethyl acetate/hexane, 3:7). Yield: 1.9 g (4.1 mmol, 56%). Mp 96–98 °C. $^1$H NMR ($CDCl_3$): $\delta$ 2.36 (s, 3H, $CH_3$), 2.50–2.56 (m, 7H, $N(CH_3)_2$, C≡CH), 2.67 (q, 2H, $CH_2CH_2$), 3.34–3.57 (m, 2H, $CH_2CH_2$), 3.81 (s, 3H, $OCH_3$), 4.72 (d, 2H, $CH_2C{\equiv}C$), 4.79 (d, 1H, CHN), 5.61 (br s, 1H, NH), 5.80 (d, 1H, NH), 6.44–7.17 (m, 7H, CH arom.). $^{13}$C NMR ($CDCl_3$): $\delta$ 22.3, 34.7, 39.5, 43.2, 45.9, 55.3, 57.2, 57.4, 74.1, 75.3, 79.8, 112.5, 113.7, 120.6, 126.2, 129.1, 129.8, 133.7, 139.4, 141.6, 144.3, 148.8, 167.0. HRMS *m/z*: Calcd for $(C_{23}H_{29}N_3O_5S+H)^+$: 460.5668. Found: 460.5671.

#### 5.4.2. 2-[(*N*,*N*′-Dimethylamino)-sulfonylamino]-*N*-[2-(3-methoxy-4-prop-2-ynyloxy-phenyl)-ethyl]-2-phenyl-acetamide (18).

Obtained from benzaldehyde (instead of *p*-tolualdehyde) according to procedures 5.4. and 5.4.1. Yield: 66%. Mp 81–83 °C. $^1$H NMR ($CDCl_3$): $\delta$ 2.42–258 (m, 7H, $N(CH_3)_2$, C≡CH), 2.69 (q, 2H, $CH_2CH_2$), 3.38–3.60 (m, 2H, $CH_2CH_2$), 3.82 (s, 3H, $OCH_3$), 4.77 (d, 2H, $CH_2C{\equiv}C$), 4.82 (d, 1H, CHN), 5.58 (br s, 1H, NH), 5.83 (d, 1H, NH), 6.44–7.39 (m, 8H, CH arom.). MS *m/z*: 446 $(C_{22}H_{27}N_3O_5S+H)^+$.

#### 5.4.3. 2-[(*N*,*N*′-Dimethylamino)-sulfonylamino]-*N*-[2-(3-methoxy-4-prop-2-ynyloxy-phenyl)-ethyl]-2-*o*-tolyl-acetamide (19).

Obtained from *o*-tolualdehyde (instead of *p*-tolualdehyde) according to procedures 5.4. and 5.4.1.

Yield: 57%. Mp 112–114 °C. $^1$H NMR ($CDCl_3$): $\delta$ 2.28 (s, 3H, $CH_3$), 2.45 (s, 6H, $N(CH_3)_2$), 2.53 (t, 1H, C≡CH), 2.64 (q, 2H, $CH_2CH_2$), 3.37–3.59 (m, 2H, $CH_2CH_2$), 3.80 (s, 3H, $OCH_3$), 4.73 (d, 2H, $CH_2C{\equiv}C$), 5.02 (d, 1H, CHN), 5.38 (br s, 1H, NH), 5.81 (d, 1H, NH), 6.42–7.29 (m, 7H, CH arom.). MS *m*/*z*: 460 $(C_{23}H_{29}N_3O_5S+H)^+$.

**5.4.4. 2-[(*N*,*N*′-Dimethylamino)-sulfonylamino]-*N*-[2-(3-methoxy-4-prop-2-ynyloxy-phenyl)-ethyl]-2-*m*-tolyl-acetamide (20).** Obtained from *m*-tolualdehyde (instead of *p*-tolualdehyde) according to procedures 5.4. and 5.4.1. Yield: 61%. Mp 119–120 °C. $^1$H NMR ($CDCl_3$): $\delta$ 2.36 (s, 3H, $CH_3$), 2.45–2.57 (m, 7H, $N(CH_3)_2$, C≡CH), 2.65 (q, 2H, $CH_2CH_2$), 3.38–3.58 (m, 2H, $CH_2CH_2$), 3.81 (s, 3H, $OCH_3$), 4.73–4.79 (m, 3H, $CH_2C{\equiv}C$, CHN), 5.57 (br s, 1H, NH), 5.79 (d, 1H, NH), 6.42–7.27 (m, 7H, CH arom.). MS *m*/*z*: 460 $(C_{23}H_{29}N_3O_5S+H)^+$.

**5.4.5. 2-[(*N*,*N*′-Dimethylamino)-sulfonylamino]-2-(4-fluoro-phenyl)-*N*-[2-(3-methoxy-4-prop-2-ynyloxyphenyl)-ethyl]-acetamide (21).** Obtained from 4-fluoro-benzaldehyde (instead of *p*-tolualdehyde) according to procedures 5.4. and 5.4.1. Yield: 68%. $^1$H NMR ($CDCl_3$): $\delta$ 2.49–2.56 (m, 7H, $N(CH_3)_2$, C≡CH), 2.68 (q, 2H, $CH_2CH_2$), 3.38–3.61 (m, 2H, $CH_2CH_2$), 3.82 (s, 3H, $OCH_3$), 4.74 (d, 2H, $CH_2C{\equiv}C$), 4.79 (d, 1H, CHN), 5.46 (br s, 1H, NH), 5.78 (d, 1H, NH), 6.44–7.25 (m, 7H, CH arom.). MS *m*/*z*: 464 $(C_{22}H_{26}FN_3O_5S+H)^+$.

**5.4.6. 2-(4-Chloro-phenyl)-2-[(*N*,*N*′-dimethylamino)-sulfonylamino]-*N*-[2-(3-methoxy-4-prop-2-ynyloxyphenyl)-ethyl]-acetamide (22).** Obtained from 4-chloro-benzaldehyde (instead of *p*-tolualdehyde) according to procedures 5.4. and 5.4.1. Yield: 65%. $^1$H NMR ($CDCl_3$): $\delta$ 2.48–2.58 (m, 7H, $N(CH_3)_2$, C≡CH), 2.65 (q, 2H, $CH_2CH_2$), 3.37–3.62 (m, 2H, $CH_2CH_2$), 3.81 (s, 3H, $OCH_3$), 4.72–4.79 (m, 3H, $CH_2C{\equiv}C$, CHN), 5.51 (br s, 1H, NH), 5.80 (d, 1H, NH), 6.41–7.38 (m, 7H, CH arom.). MS *m*/*z*: 481 $(C_{22}H_{26}ClN_3O_5S+H)^+$.

**5.4.7. 2-(4-Bromo-phenyl)-2-[(*N*,*N*′-dimethylamino)-sulfonylamino]-*N*-[2-(3-methoxy-4-prop-2-ynyloxyphenyl)-ethyl]-acetamide (23).** Obtained from 4-bromo-benzaldehyde (instead of *p*-tolualdehyde) according to procedures 5.4. and 5.4.1. Yield: 66%. Mp 115–117 °C. $^1$H NMR ($CDCl_3$): $\delta$ 2.52 (t, 1H, C≡CH), 2.56 (s, 6H, $N(CH_3)_2$), 2.67 (q, 2H, $CH_2CH_2$), 3.33–3.60 (m, 2H, $CH_2CH_2$), 3.82 (s, 3H, $OCH_3$), 4.74 (d, 2H, $CH_2C{\equiv}C$), 4.79 (d, 1H, CHN), 5.73 (br s, 1H, NH), 5.89 (d, 1H, NH), 6.41–7.48 (m, 7H, CH arom.). MS *m*/*z*: 525 $(C_{22}H_{26}BrN_3O_5S+H)^+$.

**5.4.8. 2-[(*N*,*N*′-Dimethylamino)-sulfonylamino]-*N*-[2-(3-methoxy-4-prop-2-ynyloxy-phenyl)-ethyl]-2-(4-trifluoromethyl-phenyl)-acetamide (24).** Obtained from 4-trifluoromethyl-benzaldehyde (instead of *p*-tolualdehyde) according to procedures 5.4. and 5.4.1. Yield: 62%. $^1$H NMR ($CDCl_3$): $\delta$ 2.51 (t, 1H, C≡CH), 2.58 (s, 6H, $N(CH_3)_2$), 2.66 (q, 2H, $CH_2CH_2$), 3.37–3.61 (m, 2H, $CH_2CH_2$), 3.81 (s, 3H, $OCH_3$), 4.75 (d, 2H, $CH_2C{\equiv}C$), 4.84 (d, 1H, CHN), 5.55 (br s, 1H, NH), 5.82 (d, 1H, NH), 6.41–7.64 (m, 7H, CH arom.). MS *m*/*z*: 514 $(C_{23}H_{26}F_3N_3O_5S+H)^+$.

**5.4.9. 2-[(*N*,*N*′-Dimethylamino)-sulfonylamino]-2-(4-ethyl-phenyl)-*N*-[2-(3-methoxy-4-prop-2-ynyloxyphenyl)-ethyl]-acetamide (25).** Obtained from 4-ethyl-benzaldehyde (instead of *p*-tolualdehyde) according to procedures 5.4. and 5.4.1. Yield: 65%. $^1$H NMR ($CDCl_3$): $\delta$ 1.24 (t, 3H, $CH_2CH_3$), 2.49–2.57 (m, 7H, $N(CH_3)_2$, C≡CH), 2.62–2.73 (m, 4H, $CH_2CH_2$, $CH_2CH_3$), 3.35–3.59 (m, 2H, $CH_2CH_2$), 3.82 (s, 3H, $OCH_3$), 4.73 (d, 2H, $CH_2C{\equiv}C$), 4.79 (d, 1H, CHN), 5.64 (br s, 1H, NH), 5.80 (d, 1H, NH), 6.43–7.22 (m, 7H, CH arom.). MS *m*/*z*: 474 $(C_{24}H_{31}N_3O_5S+H)^+$.

**5.4.10. 2-[(*N*,*N*′-Dimethylamino)-sulfonylamino]-2-(4-isopropyl-phenyl)-*N*-[2-(3-methoxy-4-prop-2-ynyloxyphenyl)-ethyl]-acetamide (26).** Obtained from 4-isopropyl-benzaldehyde (instead of *p*-tolualdehyde) according to procedures 5.4. and 5.4.1. Yield: 59%. Mp 97–99 °C. $^1$H NMR ($CDCl_3$): $\delta$ 1.24 (d, 6H, $CH(CH_3)_2$), 2.46–2.57 (m, 7H, $N(CH_3)_2$, C≡CH), 2.66 (q, 2H, $CH_2CH_2$), 2.91 (q, 1H, $CH(CH_3)_2$), 3.38–3.58 (m, 2H, $CH_2CH_2$), 3.81 (s, 3H, $OCH_3$), 4.72 (d, 2H, $CH_2C{\equiv}C$), 4.78 (d, 1H, CHN), 5.63 (br s, 1H, NH), 5.74 (d, 1H, NH), 6.42–7.23 (m, 7H, CH arom.). MS *m*/*z*: 488 $(C_{25}H_{33}N_3O_5S+H)^+$.

**5.4.11. 2-[(*N*,*N*′-Dimethylamino)-sulfonylamino]-*N*-[2-(3-methoxy-4-prop-2-ynyloxy-phenyl)-ethyl]-2-(4-propyl-phenyl)-acetamide (27).** Obtained from 4-propyl-benzaldehyde (instead of *p*-tolualdehyde) according to procedures 5.4. and 5.4.1. Yield: 63%. $^1$H NMR ($CDCl_3$): $\delta$ 0.94 (t, 3H, $CH_2CH_2CH_3$), 1.63 (q, 2H, $CH_2CH_2CH_3$), 2.49–2.56 (m, 7H, $N(CH_3)_2$, C≡CH), 2.62 (t, 2H, $CH_2CH_2CH_3$), 2.70 (q, 2H, $CH_2CH_2$), 3.38–3.57 (m, 2H, $CH_2CH_2$), 3.82 (s, 3H, $OCH_3$), 4.73 (d, 2H, $CH_2C{\equiv}C$), 4.78 (d, 1H, CHN), 5.61 (br s, 1H, NH), 5.78 (d, 1H, NH), 6.44–7.17 (m, 7H, CH arom.). MS *m*/*z*: 488 $(C_{25}H_{33}N_3O_5S+H)^+$.

**5.4.12. 2-(4-*tert*-Butyl-phenyl)-2-[(*N*,*N*′-dimethylamino)-sulfonylamino]-*N*-[2-(3-methoxy-4-prop-2-ynyloxyphenyl)-ethyl]-acetamide (28).** Obtained from 4-*tert*-butyl-benzaldehyde (instead of *p*-tolualdehyde) according to procedures 5.4. and 5.4.1. Yield: 54%. $^1$H NMR ($CDCl_3$): $\delta$ 1.33 (s, 9H, $C(CH_3)_3$), 2.49–2.57 (m, 7H, $N(CH_3)_2$, C≡CH), 2.70 (q, 2H, $CH_2CH_2$), 3.39–3.57 (m, 2H, $CH_2CH_2$), 3.81 (s, 3H, $OCH_3$), 4.74 (d, 2H, $CH_2C{\equiv}C$), 4.79 (d, 1H, CHN), 5.63 (br s, 1H, NH), 5.72 (d, 1H, NH), 6.44–7.40 (m, 7H, CH arom.). MS *m*/*z*: 502 $(C_{26}H_{35}N_3O_5S+H)^+$.

**5.4.13. 2-[(*N*,*N*′-Dimethylamino)-sulfonylamino]-2-(4-methoxy-phenyl)-*N*-[2-(3-methoxy-4-prop-2-ynyloxyphenyl)-ethyl]-acetamide (29).** Obtained from *p*-anisaldehyde (instead of *p*-tolualdehyde) according to procedures 5.4. and 5.4.1. Yield: 69%. $^1$H NMR ($CDCl_3$): $\delta$ 2.50–2.57 (m, 7H, $N(CH_3)_2$, C≡CH), 2.69 (q, 2H, $CH_2CH_2$), 3.36–3.58 (m, 2H, $CH_2CH_2$), 3.81 (s, 3H, $OCH_3$), 3.83 (s, 3H, $OCH_3$), 4.74–4.79 (m, 3H, $CH_2C{\equiv}C$, CHN), 5.49 (br s, 1H, NH), 5.75 (d, 1H, NH), 6.46–7.19 (m, 7H, CH arom.). MS *m*/*z*: 476 $(C_{22}H_{29}N_3O_6S+H)^+$.

**5.4.14. 2-[(*N*,*N*′-Dimethylamino)-sulfonylamino]-*N*-[2-(3-methoxy-4-prop-2-ynyloxy-phenyl)-ethyl]-2-(4-trifluoromethoxy-phenyl)-acetamide (30).** Obtained from 4-trifluoromethoxy-benzaldehyde (instead of *p*-tolualdehyde) according to procedures 5.4. and 5.4.1. Yield: 62%. $^1$H NMR ($CDCl_3$): $\delta$ 2.52 (t, 1H, C≡CH), 2.57 (s, 6H, $N(CH_3)_2$), 2.70 (q, 2H, $CH_2CH_2$), 3.39–3.62 (m, 2H, $CH_2CH_2$), 3.83 (s, 3H, $OCH_3$), 4.73 (d, 2H, $CH_2C{\equiv}C$), 4.82 (d, 1H, CHN), 5.67 (br s, 1H, NH), 5.82 (d, 1H, NH), 6.47–7.33 (m, 7H, CH arom.). MS *m*/*z*: 530 $(C_{23}H_{26}F_3N_3O_6S+H)^+$.

**5.4.15. 2-[(*N*,*N*′-Dimethylamino)-sulfonylamino]-2-(4-ethoxy-phenyl)-*N*-[2-(3-methoxy-4-prop-2-ynyloxyphenyl)-ethyl]-acetamide (31).** Obtained from 4-ethoxy-benzaldehyde (instead of *p*-tolualdehyde) according to procedures 5.4. and 5.4.1. Yield: 72%. Mp 114–115 °C. $^1$H NMR ($CDCl_3$): $\delta$ 1.43 (t, 3H, $CH_2CH_3$), 2.51–2.56 (m, 7H, $N(CH_3)_2$, C≡CH), 2.65 (q, 2H, $CH_2CH_2$), 3.36–3.59 (m, 2H, $CH_2CH_2$), 3.81 (s, 3H, $OCH_3$), 4.04 (q, 2H, $CH_2CH_3$), 4.72–4.78 (m, 4H, $CH_2C{\equiv}C$, CHN), 5.52 (br s, 1H, NH), 5.77 (d, 1H, NH), 6.43–7.09 (m, 7H, CH arom.). MS *m*/*z*: 490 $(C_{24}H_{31}N_3O_6S+H)^+$.

**5.4.16. 2-[(*N*,*N*′-Dimethylamino)-sulfonylamino]-*N*-[2-(3-methoxy-4-prop-2-ynyloxy-phenyl)-ethyl]-2-(4-methylsulfanyl-phenyl)-acetamide (32).** Obtained from 4-methylthio-benzaldehyde (instead of *p*-tolualdehyde) according to procedures 5.4. and 5.4.1. Yield: 63%. $^1$H NMR ($CDCl_3$): $\delta$ 2.48 (s, 3H, $SCH_3$), 2.51–2.56 (m, 7H, $N(CH_3)_2$, C≡CH), 2.64 (q, 2H, $CH_2CH_2$), 3.31–3.57 (m, 2H, $CH_2CH_2$), 3.80 (s, 3H, $OCH_3$), 4.72 (d, 2H, $CH_2C{\equiv}C$), 4.78 (d, 1H, CHN), 5.81 (br s, 1H, NH), 5.91 (d, 1H, NH), 6.44–7.17 (m, 7H, CH arom.). MS *m*/*z*: 492 $(C_{23}H_{29}N_3O_5S_2+H)^+$.

**5.4.17. 2-(3,4-Dichloro-phenyl)-2-[(*N*,*N*′-dimethylamino)-sulfonylamino]-*N*-[2-(3-methoxy-4-prop-2-ynyloxyphenyl)-ethyl]-acetamide (33).** Obtained from 3,4-dichloro-benzaldehyde (instead of *p*-tolualdehyde) according to procedures 5.4. and 5.4.1. Yield: 66%. Mp 131–132 °C. $^1$H NMR ($CDCl_3$): $\delta$ 2.52 (t, 1H, C≡CH), 2.59 (s, 6H, $N(CH_3)_2$), 2.70 (q, 2H, $CH_2CH_2$), 3.39–3.61 (m, 2H, $CH_2CH_2$), 3.82 (s, 3H, $OCH_3$), 4.73–4.77 (m, 3H, $CH_2C{\equiv}C$, CHN), 5.56 (br s, 1H, NH), 5.83 (d, 1H, NH), 6.44–7.45 (m, 6H, CH arom.). MS *m*/*z*: 515 $(C_{22}H_{25}Cl_2N_3O_5S+H)^+$.

**5.4.18. 2-(3-Chloro-4-fluoro-phenyl)-2-[(*N*,*N*′-dimethylamino)-sulfonylamino]-*N*-[2-(3-methoxy-4-prop-2-ynyloxyphenyl)-ethyl]-acetamide (34).** Obtained from 3-chloro-4-fluoro-benzaldehyde (instead of *p*-tolualdehyde) according to procedures 5.4. and 5.4.1. Yield: 62%. $^1$H NMR ($CDCl_3$): $\delta$ 2.50–2.57 (m, 7H, $N(CH_3)_2$, C≡CH), 2.63 (q, 2H, $CH_2CH_2$), 3.36–3.58 (m, 2H, $CH_2CH_2$), 3.79 (s, 3H, $OCH_3$), 4.68–4.75 (m, 3H, $CH_2C{\equiv}C$, CHN), 5.54 (br s, 1H, NH), 5.77 (d, 1H, NH), 6.43–7.37 (m, 6H, CH arom.). MS *m*/*z*: 499 $(C_{22}H_{25}ClFN_3O_5S+H)^+$.

**5.4.19. 2-(3,4-Difluoro-phenyl)-2-[(*N*,*N*′-dimethylamino)-sulfonylamino]-*N*-[2-(3-methoxy-4-prop-2-ynyloxyphenyl)-ethyl]-acetamide (35).** Obtained from 3,4-difluoro-benzaldehyde (instead of *p*-tolualdehyde) according to procedures 5.4. and 5.4.1. Yield: 68%. Mp 116–118 °C. $^1$H NMR ($CDCl_3$): $\delta$ 2.51 (t, 1H, C≡CH), 2.59 (s, 6H, $N(CH_3)_2$), 2.70 (q, 2H, $CH_2CH_2$), 3.37–3.58 (m, 2H, $CH_2CH_2$), 3.82 (s, 3H, $OCH_3$), 4.72 (d, 2H, $CH_2C{\equiv}C$), 4.78 (d, 1H, CHN), 5.79 (br s, 1H, NH), 5.92 (d, 1H, NH), 6.46–7.18 (m, 6H, CH arom.). MS *m*/*z*: 482 $(C_{22}H_{25}F_2N_3O_5S+H)^+$.

**5.4.20. 2-[(*N*,*N*′-Dimethylamino)-sulfonylamino]-2-(3,4-dimethyl-phenyl)-*N*-[2-(3-methoxy-4-prop-2-ynyloxyphenyl)-ethyl]-acetamide (36).** Obtained from 3,4-dimethyl-benzaldehyde (instead of *p*-tolualdehyde) according to procedures 5.4. and 5.4.1. Yield: 63%. $^1$H NMR ($CDCl_3$): $\delta$ 2.24 (s, 3H, $CH_3$), 2.27 (s, 3H, $CH_3$), 2.51–2.56 (m, 7H, $N(CH_3)_2$, C≡CH), 2.68 (q, 2H, $CH_2CH_2$), 3.38–3.53 (m, 2H, $CH_2CH_2$), 3.83 (s, 3H, $OCH_3$), 4.72–4.76 (m, 3H, $CH_2C{\equiv}C$, CHN), 5.59 (br s, 1H, NH), 5.78 (d, 1H, NH), 6.45–7.14 (m, 6H, CH arom.). MS *m*/*z*: 474 $(C_{24}H_{31}N_3O_5S+H)^+$.

### 5.5. *N*-Formyl-2,3,4,6-tetra-*O*-pivaloyl-β-D-galactopyranosyl-(*R*)-4-chlorophenylglycine-*N*′-2-(3-methoxy-4-prop-2-ynyloxyphenyl)-ethylamide (12)

To solution of 2,3,4,6-tetra-*O*-pivaloyl-β-D-galactopyranosylamine (9.13 g, 17.7 mmol), 4-chloro-benzaldehyde (3.18 g, 18.1 mmol), formic acid (0.72 ml, 19.5 mmol), 4-(2-isocyanoethyl)-2-methoxy-1-prop-2-ynyloxybenzene (**10**, 4.0 g, 18.6 mmol) in 150 ml of tetrahydrofuran was added at 0 °C a 2.23 M solution of $ZnCl_2{\cdot}OEt_2$ in dichloromethane (7.94 ml, 17.7 mmol). The mixture was stirred for 12 h during which time the temperature rose to room temperature. After evaporation of the solvents, the residue was taken up in dichloromethane and washed with a solution of sodium bicarbonate and with brine. The organic layer was dried over magnesium sulfate and evaporated. The remainder was purified by crystallisation from ethyl acetate and *n*-hexane to give the title compound as a single diastereoisomer. Its configuration (2*R*, β-D) was assigned in analogy to the literature.[19h] Yield: 8.95 g (10.0 mmol, 56%). $^1$H NMR ($CDCl_3$): $\delta$ 1.16 (s, 24H, piv), 1.26 (s, 12 H, piv), 2.47 (t, 1H, C≡CH), 2.65–2.84 (m, 2H, $CH_2CH_2$), 3.30–3.72 (m, 2H, $CH_2CH_2$), 3.79 (s, 3H, $OCH_3$), 3.84–4.01 (m, 2H, galactose), 4.11–4.21 (m, 1H, galactose), 4.73 (m, 2H, $CH_2C{\equiv}C$), 5.01 and 5.19 (2× s, 1H, CHα (2 rotamers)), 5.10–5.30 (m, 1H, galactose), 5.39–5.59 (m, 2H, galactose), 5.96 (d, 1H, CH anomeric), 6.47 (t, 1H, NH), 6.62–6.75 (m, 2H, CH arom.), 6.88–6.95 (m, 1H, CH arom.), 7.18–7.31 (m, 4H, CH arom.), 8.22 (d, 1H, CHO). MS *m*/*z*: 943 $(C_{47}H_{63}ClN_2O_{13}+HCOO)^-$.

### 5.6. (2*R*)-2-(4-Chlorophenyl)-2-ethanesulfonylamino-*N*-[2-(3-methoxy-4-prop-2-ynyloxyphenyl)-ethyl]-acetamide (13)

Compound **12** (3.0 g, 3.34 mmol) was dissolved in 20 ml of ethanol and 20 ml of a concentrated solution of HCl in methanol was added at 0 °C. After 1 h at rt, 10 ml of the concentrated HCl solution in methanol was added and the mixture was further stirred for 5 h. After the addition of 5 ml of water, the solution was stirred for 16 h at room temperature. The ethanol was evaporated

and the residue was diluted with water, washed with diethyl ether and the water phase was carefully evaporated to give 1.1 g (2.69 mmol, 81%) of brownish crystals which were directly submitted to the next step.

To a solution of 1.1 g (2.69 mmol) of the material isolated in the previous step in 40 ml THF was added ethanesulfonylchloride (0.306 ml, 3.23 mmol) and ethyldiisopropylamine (0.970 ml, 5.67 mmol) at 0 °C. The mixture was stirred for 16 h at room temperature and then poured over a 2 N HCl solution and extracted with ethyl acetate. The organic layer was washed again with 2 N HCl, dried over magnesium sulfate and evaporated. The remainder was purified by chromatography on silica gel (ethyl acetate/hexane, 6:4). Yield: 1.05 g ( 2.26 mmol, 84%). The compound was analysed on chiral HPLC (Chiralpack AD, eluent: 50% isopropanol/hexane) and compared with the racemic analogue: the retention time of the unique peak was 14.60 min as compared to 11.86 and 14.86 min for the racemate (2 peaks). No trace of the other enantiomer was found (ee: >98%).$^1$H NMR ($CDCl_3$): $\delta$ 1.18 (t, 3H, $CH_3CH_2$), 2.45 (t, 1H, C≡CH), 2.47–2.82 (m, 4H, $CH_2CH_2$, $CH_3CH_2$), 3.30–3.61 (2m, 2H, $CH_2CH_2$), 3.81 (s, 3H, $OCH_3$), 4.77 (m, 2H, $CH_2C{\equiv}C$), 4.91 (d, 1H, CHα), 5.59 (t, 1H, NH), 5.81 (d, 1H, NH), 6.42 (m, 1H, CH arom.), 6.60 (m, 1H, CH arom.), 6.84 (d, 1H, CH arom.), 7.20–7.30 (m, 2H, CH arom.), 7.35–7.41 (m, 2H, CH arom.).

### 5.7. 2-(4-Chlorophenyl)-2-hydroxy-*N*-[2-(3-methoxy-4-prop-2-ynyloxyphenyl)-ethyl]-acetamide (14)

*N*-[2-(3-Methoxy-4-prop-2-ynyloxyphenyl)-ethyl]-formamide (**9**, 34 g, 0.14 mol) and triethylamine (34 g, 0.34 mol) were dissolved in 120 ml of dichloromethane. A solution of bis(trichloromethyl)carbonate (triphosgene, 16 g, 55 mmol) in 80 ml of dichloromethane was added at 5 °C. This mixture was stirred for 4 h at 5 °C and then cooled to −78 °C. A solution of titanium tetrachloride (28 g, 0.15 mol) in 150 ml of dichloromethane was added and the mixture was stirred for 2 h at −40 °C. A solution of 4-chlorobenzaldehyde (20 g, 0.14 mol) in 70 ml of dichloromethane was added dropwise and the reaction mixture was stirred for 16 h at room temperature. Subsequently the mixture was quenched with 80 ml of 5 N hydrochloric acid, stirred for 30 min at room temperature and washed with water. The phases were separated, the organic layer was dried over magnesium sulfate and evaporated. The residue was purified by chromatography on silica gel (ethyl acetate/hexane, 1:4). Yield: 28 g (75 mmol, 54%). $^1$H NMR ($CDCl_3$): $\delta$ 2.54 (t, 1H, C≡CH), 2.72 (t, 2H, $CH_2CH_2$), 3.53 (q, 2H, $CH_2CH_2$), 3.84 (s, 3H, $OCH_3$), 4.78 (m, 2H, $CH_2C{\equiv}C$), 4.98 (s, 1H, CHOH), 6.07 (br s, 1H, NH), 6.53–7.38 (m, 7H, CH arom.). $^{13}$C NMR ($CDCl_3$): $\delta$ 21.0, 35.1, 40.5, 55.8, 56.9, 60.5, 73.4, 75.8, 78.7, 112.4, 114.6, 120.5, 128.0, 128.8, 132.4, 134.3, 138.0, 145.5, 149.7, 171.8. HRMS *m/z*: Calcd for $(C_{20}H_{20}ClNO_4+H)^+$: 374.1154. Found: 374.1156.

**5.7.1. 2-(4-Chlorophenyl)-*N*-[2-(3-methoxy-4-prop-2-ynyloxyphenyl)-ethyl]-2-prop-2-ynyloxyacetamide (6).** An 80% solution of propargyl bromide in toluene (1.2 g, 7.5 mmol) was added slowly at room temperature to a mixture of 2-(4-chlorophenyl)-2-hydroxy-*N*-[2-(3-methoxy-4-prop-2-ynyloxyphenyl)-ethyl]-acetamide (**12**, 2.6 g, 7.0 mmol), a 30% aqueous sodium hydroxide solution (3.0 ml, 30 mmol) and catalytic amounts of tetrabutylammonium bromide in 15 ml of dichloromethane. The reaction mixture was stirred for 16 h at 40 °C. Subsequently the mixture was evaporated and the residue was diluted with water and dichloromethane. The phases were separated and the aqueous layer was extracted twice with dichloromethane. The combined organic layer was washed with brine and dried over magnesium sulfate. After evaporation of the solvent, the residue was purified by silica gel chromatography (ethyl acetate/hexane, 1:5). Yield: 2.3 g (5.6 mmol, 79%). Mp 96–97 °C. $^1$H NMR ($CDCl_3$): $\delta$ 2.42 (t, 1H, C≡CH), 2.47 (t, 1H, C≡CH), 2.74 (t, 2H, $CH_2CH_2$), 3.46 (q, 2H, $CH_2CH_2$), 3.79 (s, 3H, $OCH_3$), 3.91 (dd, 1H, $CH_2C{\equiv}C$), 4.14 (dd, 1H, $CH_2C{\equiv}C$), 4.69 (d, 2H, $CH_2C{\equiv}C$), 4.91 (s, 1H, CHO), 6.62–7.29 (m, 7H, CH arom.). $^{13}$C NMR ($CDCl_3$): $\delta$ 22.3, 35.2, 39.5, 55.1, 57.4, 60.7, 72.8, 73.6, 74.7, 76.9, 78.7, 79.0, 111.8, 114.3, 121.4, 128.6, 129.1, 132.1, 133.7, 138.2, 145.5, 149.3, 169.8. HRMS *m/z*: Calcd for $(C_{23}H_{22}ClNO_4+H)^+$: 412.8848. Found: 412.8844.

**5.7.2. *N*-[2-(3-Methoxy-4-prop-2-ynyloxyphenyl)-ethyl]-2-phenyl-2-prop-2-ynyloxyacetamide (37).** Obtained from benzaldehyde (instead of 4-chloro-benzaldehyde) according to procedures 5.7. and 5.7.1. Yield: 68%. Mp 73–74 °C. $^1$H NMR ($CDCl_3$): $\delta$ 2.44 (t, 1H, C≡CH), 2.49 (t, 1H, C≡CH), 2.76 (t, 2H, $CH_2CH_2$), 3.51 (q, 2H, $CH_2CH_2$), 3.81 (s, 3H, $OCH_3$), 3.94 (dd, 1H, $CH_2C{\equiv}C$), 4.16 (dd, 1H, $CH_2C{\equiv}C$), 4.73 (d, 2H, $CH_2C{\equiv}C$), 4.97 (s, 1H, CHO), 6.66–7.32 (m, 8H, CH arom.). MS *m/z*: 378 $(C_{23}H_{23}NO_4+H)^+$.

**5.7.3. 2-(2-Chlorophenyl)-*N*-[2-(3-methoxy-4-prop-2-ynyloxyphenyl)-ethyl]-2-prop-2-ynyloxyacetamide (38).** Obtained from 2-chloro-benzaldehyde (instead of 4-chloro-benzaldehyde) according to procedures 5.7. and 5.7.1. Yield: 53%. $^1$H NMR ($CDCl_3$): $\delta$ 2.42 (t, 1H, C≡CH), 2.45 (t, 1H, C≡CH), 2.77 (t, 2H, $CH_2CH_2$), 3.52 (q, 2H, $CH_2CH_2$), 3.79 (s, 3H, $OCH_3$), 3.93 (dd, 1H, $CH_2C{\equiv}C$), 4.14 (dd, 1H, $CH_2C{\equiv}C$), 4.69 (d, 2H, $CH_2C{\equiv}C$), 5.42 (s, 1H, CHO), 6.67–7.35 (m, 7H, CH arom.). MS *m/z*: 413 $(C_{23}H_{22}ClNO_4+H)^+$.

**5.7.4. 2-(3-Fluorophenyl)-*N*-[2-(3-methoxy-4-prop-2-ynyloxyphenyl)-ethyl]-2-prop-2-ynyloxyacetamide (39).** Obtained from 3-fluoro-benzaldehyde (instead of 4-chloro-benzaldehyde) according to procedures 5.7. and 5.7.1. Yield: 63%. $^1$H NMR ($CDCl_3$): $\delta$ 2.46–2.50 (m, 2H, C≡CH), 2.78 (t, 2H, $CH_2CH_2$), 3.51 (q, 2H, $CH_2CH_2$), 3.83 (s, 3H, $OCH_3$), 3.98 (dd, 1H, $CH_2C{\equiv}C$), 4.19 (dd, 1H, $CH_2C{\equiv}C$), 4.74 (d, 2H, $CH_2C{\equiv}C$), 4.98 (s, 1H, CHO), 6.65–7.32 (m, 7H, CH arom.). MS *m/z*: 396 $(C_{23}H_{22}FNO_4+H)^+$.

**5.7.5. 2-(3-Chlorophenyl)-*N*-[2-(3-methoxy-4-prop-2-ynyloxyphenyl)-ethyl]-2-prop-2-ynyloxyacetamide (40).** Obtained from 3-chloro-benzaldehyde (instead of 4-chloro-benzaldehyde) according to procedures 5.7.

and 5.7.1. Yield: 65%. $^1$H NMR ($CDCl_3$): $\delta$ 2.48–2.53 (m, 2H, C≡CH), 2.80 (t, 2H, $CH_2CH_2$), 3.54 (q, 2H, $CH_2CH_2$), 3.84 (s, 3H, $OCH_3$), 3.98 (dd, 1H, $CH_2C{\equiv}C$), 4.21 (dd, 1H, $CH_2C{\equiv}C$), 4.77 (d, 2H, $CH_2C{\equiv}C$), 4.98 (s, 1H, CHO), 6.68–7.37 (m, 7H, CH arom.). MS *m*/*z*: 413 $(C_{23}H_{22}ClNO_4+H)^+$.

**5.7.6. 2-(3-Bromophenyl)-*N*-[2-(3-methoxy-4-prop-2-ynyloxyphenyl)-ethyl]-2-prop-2-ynyloxyacetamide (41).** Obtained from 3-bromo-benzaldehyde (instead of 4-chloro-benzaldehyde) according to procedures 5.7. and 5.7.1. Yield: 61%. $^1$H NMR ($CDCl_3$): $\delta$ 2.42–2.47 (m, 2H, C≡CH), 2.73 (t, 2H, $CH_2CH_2$), 3.46 (q, 2H, $CH_2CH_2$), 3.79 (s, 3H, $OCH_3$), 3.92 (dd, 1H, $CH_2C{\equiv}C$), 4.13 (dd, 1H, $CH_2C{\equiv}C$), 4.69 (d, 2H, $CH_2C{\equiv}C$), 4.90 (s, 1H, CHO), 6.61–7.46 (m, 7H, CH arom.). MS *m*/*z*: 457 $(C_{23}H_{22}BrNO_4+H)^+$.

**5.7.7. *N*-[2-(3-Methoxy-4-prop-2-ynyloxyphenyl)-ethyl]-2-prop-2-ynyloxy-2-*m*-tolyl-acetamide (42).** Obtained from *m*-tolualdehyde (instead of 4-chloro-benzaldehyde) according to procedures 5.7. and 5.7.1. Yield: 64%. $^1$H NMR ($CDCl_3$): $\delta$ 2.29 (s, 3H, $CH_3$), 2.41 (t, 1H, C≡CH), 2.44 (t, 1H, C≡CH), 2.73 (t, 2H, $CH_2CH_2$), 3.47 (q, 2H, $CH_2CH_2$), 3.78 (s, 3H, $OCH_3$), 3.90 (dd, 1H, $CH_2C{\equiv}C$), 4.11 (dd, 1H, $CH_2C{\equiv}C$), 4.68 (d, 2H, $CH_2C{\equiv}C$), 4.89 (s, 1H, CHO), 6.62–7.16 (m, 7H, CH arom.). MS *m*/*z*: 392 $(C_{24}H_{25}NO_4+H)^+$.

**5.7.8. *N*-[2-(3-Methoxy-4-prop-2-ynyloxyphenyl)-ethyl]-2-prop-2-ynyloxy-2-(3-trifluoromethyl-phenyl)-acetamide (43).** Obtained from 3-trifluoromethyl-benzaldehyde (instead of 4-chloro-benzaldehyde) according to procedures 5.7. and 5.7.1. Yield: 55%. Mp 89–91 °C. $^1$H NMR ($CDCl_3$): $\delta$ 2.42–2.47 (m, 2H, C≡CH), 2.73 (t, 2H, $CH_2CH_2$), 3.47 (q, 2H, $CH_2CH_2$), 3.79 (s, 3H, $OCH_3$), 3.93 (dd, 1H, $CH_2C{\equiv}C$), 4.16 (dd, 1H, $CH_2C{\equiv}C$), 4.69 (d, 2H, $CH_2C{\equiv}C$), 5.00 (s, 1H, CHO), 6.61–7.58 (m, 7H, CH arom.). MS *m*/*z*: 446 $(C_{24}H_{22}F_3NO_4+H)^+$.

**5.7.9. 2-(3-Methoxyphenyl)-*N*-[2-(3-methoxy-4-prop-2-ynyloxyphenyl)-ethyl]-2-prop-2-ynyloxyacetamide (44).** Obtained from *m*-anisaldehyde (instead of 4-chloro-benzaldehyde) according to procedures 5.7. and 5.7.1. Yield: 61%. $^1$H NMR ($CDCl_3$): $\delta$ 2.44 (t, 1H, C≡CH), 2.48 (t, 1H, C≡CH), 2.76 (t, 2H, $CH_2CH_2$), 3.49 (q, 2H, $CH_2CH_2$), 3.78 (s, 3H, $OCH_3$), 3.83 (s, 3H, $OCH_3$), 3.94 (dd, 1H, $CH_2C{\equiv}C$), 4.15 (dd, 1H, $CH_2C{\equiv}C$), 4.72 (d, 2H, $CH_2C{\equiv}C$), 4.93 (s, 1H, CHO), 6.65–7.27 (m, 7H, CH arom.). MS *m*/*z*: 408 $(C_{24}H_{25}NO_5+H)^+$.

**5.7.10. 2-(4-Fluorophenyl)-*N*-[2-(3-methoxy-4-prop-2-ynyloxyphenyl)-ethyl]-2-prop-2-ynyloxyacetamide (45).** Obtained from 4-fluoro-benzaldehyde (instead of 4-chloro-benzaldehyde) according to procedures 5.7. and 5.7.1. Yield: 59%. Mp 64–66 °C. $^1$H NMR ($CDCl_3$): $\delta$ 2.41–2.48 (m, 2H, C≡CH), 2.74 (t, 2H, $CH_2CH_2$), 3.49 (q, 2H, $CH_2CH_2$), 3.80 (s, 3H, $OCH_3$), 3.91 (dd, 1H, $CH_2C{\equiv}C$), 4.13 (dd, 1H, $CH_2C{\equiv}C$), 4.71 (d, 2H, $CH_2C{\equiv}C$), 4.92 (s, 1H, CHO), 6.63–7.27 (m, 7H, CH arom.). MS *m*/*z*: 396 $(C_{23}H_{22}FNO_4+H)^+$.

**5.7.11. 2-(4-Bromophenyl)-*N*-[2-(3-methoxy-4-prop-2-ynyloxyphenyl)-ethyl]-2-prop-2-ynyloxyacetamide (46).** Obtained from 4-bromo-benzaldehyde (instead of 4-chloro-benzaldehyde) according to procedures 5.7. and 5.7.1. Yield: 62%. Mp 92–93 °C. $^1$H NMR ($CDCl_3$): $\delta$ 2.50 (t, 1H, C≡CH), 2.54 (t, 1H, C≡CH), 2.81 (t, 2H, $CH_2CH_2$), 3.54 (q, 2H, $CH_2CH_2$), 3.85 (s, 3H, $OCH_3$), 3.99 (dd, 1H, $CH_2C{\equiv}C$), 4.21 (dd, 1H, $CH_2C{\equiv}C$), 4.78 (d, 2H, $CH_2C{\equiv}C$), 4.96 (s, 1H, CHO), 6.70–7.52 (m, 7H, CH arom.). MS *m*/*z*: 457 $(C_{23}H_{22}BrNO_4+H)^+$.

**5.7.12. *N*-[2-(3-Methoxy-4-prop-2-ynyloxyphenyl)-ethyl]-2-prop-2-ynyloxy-2-p-tolyl-acetamide (47).** Obtained from *p*-tolualdehyde (instead of 4-chloro-benzaldehyde) according to procedures 5.7. and 5.7.1. Yield: 71%. Mp 72–73 °C. $^1$H NMR ($CDCl_3$): $\delta$ 2.37 (s, 3H, $CH_3$), 2.49 (t, 1H, C≡CH), 2.53 (t, 1H, C≡CH), 2.82 (t, 2H, $CH_2CH_2$), 3.55 (q, 2H, $CH_2CH_2$), 3.86 (s, 3H, $OCH_3$), 3.97 (dd, 1H, $CH_2C{\equiv}C$), 4.19 (dd, 1H, $CH_2C{\equiv}C$), 4.79 (d, 2H, $CH_2C{\equiv}C$), 4.98 (s, 1H, CHO), 6.71–7.25 (m, 7H, CH arom.). MS *m*/*z*: 392 $(C_{24}H_{25}NO_4+H)^+$.

**5.7.13. *N*-[2-(3-Methoxy-4-prop-2-ynyloxyphenyl)-ethyl]-2-prop-2-ynyloxy-2-(4-trifluoromethyl-phenyl)-acetamide (48).** Obtained from 4-trifluoromethyl-benzaldehyde (instead of 4-chloro-benzaldehyde) according to procedures 5.7. and 5.7.1. Yield: 57%. $^1$H NMR ($CDCl_3$): $\delta$ 2.45–2.49 (m, 2H, C≡CH), 2.78 (t, 2H, $CH_2CH_2$), 3.50 (q, 2H, $CH_2CH_2$), 3.81 (s, 3H, $OCH_3$), 3.96 (dd, 1H, $CH_2C{\equiv}C$), 4.19 (dd, 1H, $CH_2C{\equiv}C$), 4.73 (d, 2H, $CH_2C{\equiv}C$), 5.02 (s, 1H, CHO), 6.63–7.59 (m, 7H, CH arom.). MS *m*/*z*: 446 $(C_{24}H_{22}F_3NO_4+H)^+$.

**5.7.14. 2-(4-Methoxymethyl-phenyl)-*N*-[2-(3-methoxy-4-prop-2-ynyloxyphenyl)-ethyl]-2-prop-2-ynyloxyacetamide (49).** Obtained from 4-methoxymethyl-benzaldehyde (instead of 4-chloro-benzaldehyde) according to procedures 5.7. and 5.7.1. Yield: 64%. $^1$H NMR ($CDCl_3$): $\delta$ 2.48 (t, 1H, C≡CH), 2.52 (t, 1H, C≡CH), 2.80 (t, 2H, $CH_2CH_2$), 3.41 (s, 3H, $CH_2OCH_3$), 3.56 (q, 2H, $CH_2CH_2$), 3.85 (s, 3H, $OCH_3$), 3.97 (dd, 1H, $CH_2C{\equiv}C$), 4.18 (dd, 1H, $CH_2C{\equiv}C$), 4.48 (s, 2H, $CH_2OCH_3$), 4.77 (d, 2H, $CH_2C{\equiv}C$), 5.02 (s, 1H, CHO), 6.69–7.33 (m, 7H, CH arom.). MS *m*/*z*: 422 $(C_{25}H_{27}NO_5+H)^+$.

**5.7.15. 2-(4-Ethyl-phenyl)-*N*-[2-(3-methoxy-4-prop-2-ynyloxyphenyl)-ethyl]-2-prop-2-ynyloxyacetamide (50).** Obtained from 4-ethyl-benzaldehyde (instead of 4-chloro-benzaldehyde) according to procedures 5.7. and 5.7.1. Yield: 69%. $^1$H NMR ($CDCl_3$): $\delta$ 1.14 (t, 3H, $CH_2CH_3$), 2.41 (t, 1H, C≡CH), 2.46 (t, 1H, C≡CH), 2.59 (q, 2H, $CH_2CH_3$), 2.74 (t, 2H, $CH_2CH_2$), 3.47 (q, 2H, $CH_2CH_2$), 3.79 (s, 3H, $OCH_3$), 3.90 (dd, 1H, $CH_2C{\equiv}C$), 4.11 (dd, 1H, $CH_2C{\equiv}C$), 4.69 (d, 2H, $CH_2C{\equiv}C$), 4.92 (s, 1H, CHO), 6.63–7.19 (m, 7H, CH arom.). MS *m*/*z*: 406 $(C_{25}H_{27}NO_4+H)^+$.

**5.7.16. *N*-[2-(3-Methoxy-4-prop-2-ynyloxyphenyl)-ethyl]-2-prop-2-ynyloxy-2-(4-vinyl-phenyl)-acetamide (51).** Obtained from 4-vinyl-benzaldehyde (instead of 4-chloro-benzaldehyde) according to procedures 5.7. and 5.7.1. Yield: 50%. $^1$H NMR ($CDCl_3$): $\delta$ 2.49 (t, 1H, C≡CH), 2.53 (t, 1H, C≡CH), 2.82 (t, 2H, $CH_2CH_2$), 3.54 (q,

2H, $CH_2CH_2$), 3.85 (s, 3H, $OCH_3$), 4.00 (dd, 1H, $CH_2C{\equiv}C$), 4.21 (dd, 1H, $CH_2C{\equiv}C$), 4.78 (d, 2H, $CH_2C{\equiv}C$), 5.01 (s, 1H, CHO), 5.27 (d, 1H, $CH{=}CH_2$), 5.76 (d, 1H, $CH{=}CH_2$), 6.68–7.42 (m, 8H, CH arom., $CH{=}CH_2$). MS *m/z*: 404 $(C_{25}H_{25}NO_4+H)^+$.

**5.7.17. *N*-[2-(3-Methoxy-4-prop-2-ynyloxyphenyl)-ethyl]-2-(4-propyl-phenyl)-2-prop-2-ynyloxyacetamide (52).** Obtained from 4-propyl-benzaldehyde (instead of 4-chloro-benzaldehyde) according to procedures 5.7. and 5.7.1. Yield: 66%. $^1$H NMR ($CDCl_3$): $\delta$ 0.93 (t, 3H, $CH_2CH_2CH_3$), 1.55–1.68 (m, 2H, $CH_2CH_2CH_3$), 2.45 (t, 1H, C≡CH), 2.49 (t, 1H, C≡CH), 2.54 (q, 2H, $CH_2CH_2CH_3$), 2.80 (t, 2H, $CH_2CH_2$), 3.52 (q, 2H, $CH_2CH_2$), 3.80 (s, 3H, $OCH_3$), 3.92 (dd, 1H, $CH_2C{\equiv}C$), 4.13 (dd, 1H, $CH_2C{\equiv}C$), 4.74 (d, 2H, $CH_2C{\equiv}C$), 4.95 (s, 1H, CHO), 6.68–7.24 (m, 7H, CH arom.). MS *m/z*: 420 $(C_{26}H_{29}NO_4+H)^+$.

**5.7.18. 2-(4-Isopropyl-phenyl)-*N*-[2-(3-methoxy-4-prop-2-ynyloxyphenyl)-ethyl]-2-prop-2-ynyloxyacetamide (53).** Obtained from 4-isopropyl-benzaldehyde (instead of 4-chloro-benzaldehyde) according to procedures 5.7. and 5.7.1. Yield: 60%. $^1$H NMR ($CDCl_3$): $\delta$ 1.22 (s, 3H, $CH(CH_3)_2$), 1.25 (s, 3H, $CH(CH_3)_2$), 2.46 (t, 1H, C≡CH), 2.51 (t, 1H, C≡CH), 2.80 (t, 2H, $CH_2CH_2$), 2.89 (q, 1H, $CH(CH_3)_2$), 3.53 (q, 2H, $CH_2CH_2$), 3.82 (s, 3H, $OCH_3$), 3.94 (dd, 1H, $CH_2C{\equiv}C$), 4.16 (dd, 1H, $CH_2C{\equiv}C$), 4.75 (d, 2H, $CH_2C{\equiv}C$), 4.96 (s, 1H, CHO), 6.68–7.25 (m, 7H, CH arom.). MS *m/z*: 420 $(C_{26}H_{29}NO_4+H)^+$.

**5.7.19. 2-(4-Butyl-phenyl)-*N*-[2-(3-methoxy-4-prop-2-ynyloxyphenyl)-ethyl]-2-prop-2-ynyloxyacetamide (54).** Obtained from 4-butyl-benzaldehyde (instead of 4-chloro-benzaldehyde) according to procedures 5.7. and 5.7.1. Yield: 58%. $^1$H NMR ($CDCl_3$): $\delta$ 0.95 (t, 3H, $CH_2CH_2CH_2CH_3$), 1.37–1.62 (m, 4H, $CH_2CH_2CH_2CH_3$), 2.49 (t, 1H, C≡CH), 2.53 (t, 1H, C≡CH), 2.61 (t, 2H, $CH_2CH_2CH_2CH_3$), 2.82 (t, 2H, $CH_2CH_2$), 3.56 (q, 2H, $CH_2CH_2$), 3.87 (s, 3H, $OCH_3$), 3.96 (dd, 1H, $CH_2C{\equiv}C$), 4.18 (dd, 1H, $CH_2C{\equiv}C$), 4.77 (d, 2H, $CH_2C{\equiv}C$), 4.98 (s, 1H, CHO), 6.70–7.29 (m, 7H, CH arom.). MS *m/z*: 434 $(C_{27}H_{31}NO_4+H)^+$.

**5.7.20. 2-(4-Methoxyphenyl)-*N*-[2-(3-methoxy-4-prop-2-ynyloxyphenyl)-ethyl]-2-prop-2-ynyloxyacetamide (55).** Obtained from *p*-anisaldehyde (instead of 4-chloro-benzaldehyde) according to procedures 5.7. and 5.7.1. Yield: 67%. Mp 101–102 °C. $^1$H NMR ($CDCl_3$): $\delta$ 2.43 (t, 1H, C≡CH), 2.48 (t, 1H, C≡CH), 2.79 (t, 2H, $CH_2CH_2$), 3.51 (q, 2H, $CH_2CH_2$), 3.77 (s, 3H, $OCH_3$), 3.81 (s, 3H, $OCH_3$), 3.91 (dd, 1H, $CH_2C{\equiv}C$), 4.12 (dd, 1H, $CH_2C{\equiv}C$), 4.73 (d, 2H, $CH_2C{\equiv}C$), 4.92 (s, 1H, CHO), 6.67–7.23 (m, 7H, CH arom.). MS *m/z*: 408 $(C_{24}H_{25}NO_5+H)^+$.

**5.7.21. *N*-[2-(3-Methoxy-4-prop-2-ynyloxyphenyl)-ethyl]-2-(4-methylsulfanyl-phenyl)-2-prop-2-ynyloxyacetamide (56).** Obtained from 4-methylsulfanyl-benzaldehyde (instead of 4-chloro-benzaldehyde) according to procedures 5.7. and 5.7.1. Yield: 59%. $^1$H NMR ($CDCl_3$): $\delta$ 2.42–2.45 (m, 4H, $SCH_3$, C≡CH), 2.48 (t, 1H, C≡CH), 2.76 (t, 2H, $CH_2CH_2$), 3.50 (q, 2H, $CH_2CH_2$), 3.80 (s, 3H, $OCH_3$), 3.92 (dd, 1H, $CH_2C{\equiv}C$), 4.13 (dd, 1H, $CH_2C{\equiv}C$), 4.72 (d, 2H, $CH_2C{\equiv}C$), 4.91 (s, 1H, CHO), 6.65–7.19 (m, 7H, CH arom.). MS *m/z*: 424 $(C_{24}H_{25}NO_4S+H)^+$.

**5.7.22. 2-(2,3-Dichloro-phenyl)-*N*-[2-(3-methoxy-4-prop-2-ynyloxyphenyl)-ethyl]-2-prop-2-ynyloxyacetamide (57).** Obtained from 2,3-dichloro-benzaldehyde (instead of 4-chloro-benzaldehyde) according to procedures 5.7. and 5.7.1. Yield: 52%. $^1$H NMR ($CDCl_3$): $\delta$ 2.49–2.53 (m, 2H, C≡CH), 2.83 (t, 2H, $CH_2CH_2$), 3.59 (q, 2H, $CH_2CH_2$), 3.86 (s, 3H, $OCH_3$), 4.00 (dd, 1H, $CH_2C{\equiv}C$), 4.21 (dd, 1H, $CH_2C{\equiv}C$), 4.77 (d, 2H, $CH_2C{\equiv}C$), 5.53 (s, 1H, CHO), 6.72–7.48 (m, 6H, CH arom.). MS *m/z*: 447 $(C_{23}H_{21}Cl_2NO_4+H)^+$.

**5.7.23. 2-(3,4-Dichloro-phenyl)-*N*-[2-(3-methoxy-4-prop-2-ynyloxyphenyl)-ethyl]-2-prop-2-ynyloxyacetamide (58).** Obtained from 3,4-dichloro-benzaldehyde (instead of 4-chloro-benzaldehyde) according to procedures 5.7. and 5.7.1. Yield: 61%. $^1$H NMR ($CDCl_3$): $\delta$ 2.42–2.47 (m, 2H, C≡CH), 2.73 (t, 2H, $CH_2CH_2$), 3.47 (q, 2H, $CH_2CH_2$), 3.79 (s, 3H, $OCH_3$), 3.93 (dd, 1H, $CH_2C{\equiv}C$), 4.14 (dd, 1H, $CH_2C{\equiv}C$), 4.69 (d, 2H, $CH_2C{\equiv}C$), 4.90 (s, 1H, CHO), 6.61–7.42 (m, 6H, CH arom.). MS *m/z*: 447 $(C_{23}H_{21}Cl_2NO_4+H)^+$.

**5.7.24. 2-(2,4-Difluoro-phenyl)-*N*-[2-(3-methoxy-4-prop-2-ynyloxyphenyl)-ethyl]-2-prop-2-ynyloxyacetamide (59).** Obtained from 2,4-difluoro-benzaldehyde (instead of 4-chloro-benzaldehyde) according to procedures 5.7. and 5.7.1. Yield: 56%. $^1$H NMR ($CDCl_3$): $\delta$ 2.49–2.53 (m, 2H, C≡CH), 2.84 (t, 2H, $CH_2CH_2$), 3.58 (q, 2H, $CH_2CH_2$), 3.88 (s, 3H, $OCH_3$), 3.99 (dd, 1H, $CH_2C{\equiv}C$), 4.20 (dd, 1H, $CH_2C{\equiv}C$), 4.78 (d, 2H, $CH_2C{\equiv}C$), 5.25 (s, 1H, CHO), 6.73–7.23 (m, 6H, CH arom.). MS *m/z*: 414 $(C_{23}H_{21}F_2NO_4+H)^+$.

**5.7.25. 2-(4-Bromo-2-fluoro-phenyl)-*N*-[2-(3-methoxy-4-prop-2-ynyloxyphenyl)-ethyl]-2-prop-2-ynyloxyacetamide (60).** Obtained from 4-bromo-2-fluoro-benzaldehyde (instead of 4-chloro-benzaldehyde) according to procedures 5.7. and 5.7.1. Yield: 61%. $^1$H NMR ($CDCl_3$): $\delta$ 2.49–2.55 (m, 2H, C≡CH), 2.83 (t, 2H, $CH_2CH_2$), 3.59 (q, 2H, $CH_2CH_2$), 3.87 (s, 3H, $OCH_3$), 3.99 (dd, 1H, $CH_2C{\equiv}C$), 4.22 (dd, 1H, $CH_2C{\equiv}C$), 4.79 (d, 2H, $CH_2C{\equiv}C$), 5.23 (s, 1H, CHO), 6.74–7.31 (m, 6H, CH arom.). MS *m/z*: 475 $(C_{23}H_{21}BrFNO_4+H)^+$.

**5.7.26. 2-(3-Chloro-4-methyl-phenyl)-*N*-[2-(3-methoxy-4-prop-2-ynyloxyphenyl)-ethyl]-2-prop-2-ynyloxyacetamide (61).** Obtained from 3-chloro-*p*-tolualdehyde (instead of 4-chloro-benzaldehyde) according to procedures 5.7. and 5.7.1. Yield: 58%. $^1$H NMR ($CDCl_3$): $\delta$ 2.41 (s, 3H, $CH_3$), 2.52–2.57 (m, 2H, C≡CH), 2.84 (t, 2H, $CH_2CH_2$), 3.57 (q, 2H, $CH_2CH_2$), 3.88 (s, 3H, $OCH_3$), 4.00 (dd, 1H, $CH_2C{\equiv}C$), 4.23 (dd, 1H, $CH_2C{\equiv}C$), 4.79 (d, 2H, $CH_2C{\equiv}C$), 4.98 (s, 1H, CHO), 6.72–7.39 (m, 6H, CH arom.). MS *m/z*: 427 $(C_{24}H_{24}ClNO_4+H)^+$.

**5.7.27. 2-(3,4-Dimethyl-phenyl)-*N*-[2-(3-methoxy-4-prop-2-ynyloxyphenyl)-ethyl]-2-prop-2-ynyloxyacetamide (62).** Obtained from 3,4-dimethyl-benzaldehyde (instead of 4-

chloro-benzaldehyde) according to procedures 5.7. and 5.7.1. Yield: 66%. $^1$H NMR ($CDCl_3$): $\delta$ 2.26 (s, 6H, $CH_3$), 2.49 (t, 1H, C≡CH), 2.52 (t, 1H, C≡CH), 2.83 (t, 2H, $CH_2CH_2$), 3.54 (q, 2H, $CH_2CH_2$), 3.86 (s, 3H, $OCH_3$), 3.97 (dd, 1H, $CH_2C$≡C), 4.18 (dd, 1H, $CH_2C$≡C), 4.78 (d, 2H, $CH_2C$≡C), 4.94 (s, 1H, CHO), 6.72–7.14 (m, 6H, CH arom.). MS *m*/*z*: 406 $(C_{25}H_{27}NO_4+H)^+$.

**5.7.28. 2-(3,5-Dimethyl-phenyl)-*N*-[2-(3-methoxy-4-prop-2-ynyloxyphenyl)-ethyl]-2-prop-2-ynyloxyacetamide (63).** Obtained from 3,5-dimethyl-benzaldehyde (instead of 4-chloro-benzaldehyde) according to procedures 5.7. and 5.7.1. Yield: 63%. $^1$H NMR ($CDCl_3$): $\delta$ 2.37 (s, 6H, $CH_3$), 2.53 (t, 1H, C≡CH), 2.58 (t, 1H, C≡CH), 2.86 (t, 2H, $CH_2CH_2$), 3.59 (q, 2H, $CH_2CH_2$), 3.90 (s, 3H, $OCH_3$), 4.02 (dd, 1H, $CH_2C$≡C), 4.21 (dd, 1H, $CH_2C$≡C), 4.81 (d, 2H, $CH_2C$≡C), 4.96 (s, 1H, CHO), 6.76–7.05 (m, 6H, CH arom.). MS *m*/*z*: 406 $(C_{25}H_{27}NO_4+H)^+$.

**5.7.29. *N*-[2-(3-Methoxy-4-prop-2-ynyloxyphenyl)-ethyl]-2-prop-2-ynyloxy-2-(3,4,5-trifluoro-phenyl)-acetamide (64).** Obtained from 3,4,5-trifluoro-benzaldehyde (instead of 4-chloro-benzaldehyde) according to procedures 5.7. and 5.7.1. Yield: 58%. $^1$H NMR ($CDCl_3$): $\delta$ 2.50–2.53 (m, 2H, C≡CH), 2.81 (t, 2H, $CH_2CH_2$), 3.54 (q, 2H, $CH_2CH_2$), 3.87 (s, 3H, $OCH_3$), 4.02 (dd, 1H, $CH_2C$≡C), 4.24 (dd, 1H, $CH_2C$≡C), 4.78 (d, 2H, $CH_2C$≡C), 4.93 (s, 1H, CHO), 6.69–7.06 (m, 5H, CH arom.). MS *m*/*z*: 432 $(C_{23}H_{20}F_3NO_4+H)^+$.

**5.7.30. *N*-[2-(3-Methoxy-4-prop-2-ynyloxyphenyl)-ethyl]-2-prop-2-ynyloxy-2-(2,3,5-trichloro-phenyl)-acetamide (65).** Obtained from 2,3,5-trichloro-benzaldehyde (instead of 4-chloro-benzaldehyde) according to procedures 5.7. and 5.7.1. Yield: 56%. $^1$H NMR ($CDCl_3$): $\delta$ 2.50–2.54 (m, 2H, C≡CH), 2.85 (t, 2H, $CH_2CH_2$), 3.58 (q, 2H, $CH_2CH_2$), 3.90 (s, 3H, $OCH_3$), 4.02 (dd, 1H, $CH_2C$≡C), 4.27 (dd, 1H, $OCH_2$), 4.77 (d, 2H, $CH_2C$≡C), 5.52 (s, 1H, CHO), 6.72–7.48 (m, 5H, CH arom.). MS *m*/*z*: 482 $(C_{23}H_{20}Cl_3NO_4+H)^+$.

**5.7.31. 2-Cyclohexyl-*N*-[2-(3-methoxy-4-prop-2-ynyloxyphenyl)-ethyl]-2-prop-2-ynyloxyacetamide (66).** Obtained from cyclohexanecarbaldehyde (instead of 4-chloro-benzaldehyde) according to procedures 5.7. and 5.7.1. Yield: 47%. $^1$H NMR ($CDCl_3$): $\delta$ 1.02–1.26 (m, 6H, cyclohexyl), 1.47–1.75 (m, 5H, cyclohexyl), 2.38 (t, 1H, C≡CH), 2.48 (t, 1H, C≡CH), 2.77 (t, 2H, $CH_2CH_2$), 3.52 (q, 2H, $CH_2CH_2$), 3.68 (d, 1H, CHOH), 3.83 (s, 3H, $OCH_3$), 4.02 (dd, 2H, $CH_2C$≡C), 4.71 (d, 2H, $CH_2C$≡C), 6.69–6.95 (m, 3H, CH arom.). MS *m*/*z*: 384 $(C_{23}H_{29}NO_4+H)^+$.

**5.7.32. *N*-[2-(3-Methoxy-4-prop-2-ynyloxyphenyl)-ethyl]-2-prop-2-ynyloxy-3-(2,6,6-trimethyl-cyclohex-1-enyl)-propionamide (67).** Obtained from (2,6,6-trimethyl-cyclohex-1-enyl)-acetaldehyde (instead of 4-chloro-benzaldehyde) according to procedures 5.7. and 5.7.1. Yield: 60%. $^1$H NMR ($CDCl_3$): $\delta$ 1.04 (s, 3H, $CH_3$), 1.09 (s, 3H, $CH_3$), 1.46 (dd, 2H, cyclohexenyl), 1.61 (t, 2H, cyclohexenyl), 1.70 (s, 3H, $CH_3$), 1.94 (dd, 2H, cyclohexenyl), 2.29–2.40 (m, 2H, C≡CH, $CH_2CHO$), 2.52 (t, 1H, C≡CH), 2.63 (dd, 1H, $CH_2CHO$), 2.82 (t, 2H, $CH_2CH_2$), 3.53 (q, 2H, $CH_2CH_2$), 3.88 (s, 3H, $OCH_3$), 4.01–4.09 (m, 3H, $CH_2C$≡C, CHO), 4.75 (d, 2H, $CH_2C$≡C), 6.73–7.02 (m, 3H, CH arom.). MS *m*/*z*: 438 $(C_{27}H_{35}NO_4+H)^+$.

**5.7.33. 3-(4-Chlorophenyl)-*N*-[2-(3-methoxy-4-prop-2-ynyloxyphenyl)-ethyl]-2-prop-2-ynyloxypropionamide (68).** Obtained from (4-chlorophenyl)-acetaldehyde (instead of 4-chloro-benzaldehyde) according to procedures 5.7. and 5.7.1. Yield: 50%. $^1$H NMR ($CDCl_3$): $\delta$ 2.40 (t, 1H, C≡CH), 2.51 (t, 1H, C≡CH), 2.70 (q, 2H, $CH_2CH_2$), 2.93 (dd, 1H, $CH_2CHO$), 3.15 (dd, 1H, $CH_2CHO$), 3.49 (q, 2H, $CH_2CH_2$), 3.87 (s, 3H, $OCH_3$), 4.03 (dd, 2H, $CH_2C$≡C) 4.14 (dd, 1H, CHO), 4.75 (d, 2H, $CH_2C$≡C), 6.62–7.29 (m, 7H, CH arom.). MS *m*/*z*: 427 $(C_{24}H_{24}ClNO_4+H)^+$.

**5.7.34. 3-(4-Chloro-phenoxy)-*N*-[2-(3-methoxy-4-prop-2-ynyloxyphenyl)-ethyl]-2-prop-2-ynyloxy-propionamide (69).** Obtained from (4-chlorophenoxy)-acetaldehyde (instead of 4-chloro-benzaldehyde) according to procedures 5.7. and 5.7.1. Yield: 59%. Mp 99–100 °C. $^1$H NMR ($CDCl_3$): $\delta$ 2.39 (t, 1H, C≡CH), 2.43 (t, 1H, C≡CH), 2.72 (t, 2H, $CH_2CH_2$), 3.49 (q, 2H, $CH_2CH_2$), 3.80 (s, 3H, $OCH_3$), 4.01–4.33 (m, 5H, $OCH_2$, $CH_2C$≡C, CHO), 4.68 (d, 2H, $CH_2C$≡C), 6.66–7.19 (m, 7H, CH arom.). MS *m*/*z*: 443 $(C_{24}H_{24}ClNO_5+H)^+$.

**5.7.35. *N*-[2-(3-Methoxy-4-prop-2-ynyloxyphenyl)-ethyl]-2-prop-2-ynyloxy-3-*p*-tolyloxy-propionamide (70).** Obtained from *p*-tolyloxy-acetaldehyde (instead of 4-chloro-benzaldehyde) according to procedures 5.7. and 5.7.1. Yield: 53%. Mp 82–83 °C. $^1$H NMR ($CDCl_3$): $\delta$ 2.30 (s, 3H, $CH_3$), 2.48 (t, 1H, C≡CH), 2.53 (t, 1H, C≡CH), 2.82 (t, 2H, $CH_2CH_2$), 3.58 (q, 2H, $CH_2CH_2$), 3.89 (s, 3H, $OCH_3$), 4.13–4.42 (m, 5H, $OCH_2$, $CH_2C$≡C, CHO), 4.76 (d, 2H, $CH_2C$≡C), 6.73–7.10 (m, 7H, CH arom.). MS *m*/*z*: 422 $(C_{25}H_{27}NO_5+H)^+$.

**5.7.36. 3-Benzyloxy-*N*-[2-(3-methoxy-4-prop-2-ynyloxyphenyl)-ethyl]-2-prop-2-ynyloxypropionamide (71).** Obtained from benzyloxy-acetaldehyde (instead of 4-chloro-benzaldehyde) according to procedures 5.7. and 5.7.1. Yield: 48%. $^1$H NMR ($CDCl_3$): $\delta$ 2.36 (t, 1H, C≡CH), 2.42 (t, 1H, C≡CH), 2.71 (t, 2H, $CH_2CH_2$), 3.48 (q, 2H, $CH_2CH_2$), 3.69 (dd, 1H, $CH_2CHO$), 3.77–3.83 (m, 4H, $OCH_3$, $CH_2CHO$), 4.14 (dd, 1H, CHO), 4.20 (dd, 2H, $CH_2C$≡C), 4.49 (s, 2H, $CH_2O$), 4.67 (d, 2H, $CH_2C$≡C), 6.63–7.29 (m, 8H, CH arom.). MS *m*/*z*: 422 $(C_{25}H_{27}NO_5+H)^+$.

**5.7.37. 2-(2,3-Dihydro-benzo[1,4]dioxin-6-yl)-*N*-[2-(3-methoxy-4-prop-2-ynyloxyphenyl)-ethyl]-2-prop-2-ynyloxy-acetamide (72).** Obtained from 2,3-dihydro-benzo[1,4]dioxine-6-carbaldehyde (instead of 4-chloro-benzaldehyde) according to procedures 5.7. and 5.7.1. Yield: 59%. $^1$H NMR ($CDCl_3$): $\delta$ 2.38 (t, 1H, C≡CH), 2.42 (t, 1H, C≡CH), 2.71 (t, 2H, $CH_2CH_2$), 3.44 (q, 2H, $CH_2CH_2$), 3.78 (s, 3H, $OCH_3$), 3.86 (dd, 1H, $CH_2C$≡C), 4.06 (dd, 1H, $CH_2C$≡C), 4.15 (s, 4H, $OCH_2$-$CH_2O$), 4.66 (d, 2H, $CH_2C$≡C), 4.80 (s, 1H, CHO),

6.61–6.90 (m, 6H, CH arom.). MS *m/z*: 436 $(C_{25}H_{25}NO_6+H)^+$.

**5.7.38. 2-(9*H*-Fluorene-2-yl)-*N*-[2-(3-methoxy-4-prop-2-ynyloxyphenyl)-ethyl]-2-prop-2-ynyloxyacetamide (73).** Obtained from 9*H*-fluorene-2-carbaldehyde (instead of 4-chloro-benzaldehyde) according to procedures 5.7. and 5.7.1. Yield: 63%. $^1$H NMR ($CDCl_3$): $\delta$ 2.50–2.54 (m, 2H, C≡CH), 2.85 (t, 2H, $CH_2CH_2$), 3.59 (q, 2H, $CH_2CH_2$), 3.88 (s, 3H, $OCH_3$), 3.92 (s, 2H, fluorenyl), 4.03 (dd, 1H, $OCH_2$), 4.22 (dd, 1H, $OCH_2$), 4.76 (d, 2H, $OCH_2$), 5.10 (s, 1H, CHO), 6.71–7.82 (m, 10H, CH arom.). MS *m/z*: 466 $(C_{30}H_{27}NO_4+H)^+$.

**5.7.39. *N*-[2-(3-Methoxy-4-prop-2-ynyloxyphenyl)-ethyl]-2-prop-2-ynyloxy-2-thiophen-2-yl-acetamide (74).** Obtained from thiophene-2-carbaldehyde (instead of 4-chloro-benzaldehyde) according to procedures 5.7. and 5.7.1. Yield: 45%. $^1$H NMR ($CDCl_3$): $\delta$ 2.48–2.53 (m, 2H, C≡CH), 2.82 (t, 2H, $CH_2CH_2$), 3.57 (q, 2H, $CH_2CH_2$), 3.84 (s, 3H, $OCH_3$), 4.06 (dd, 1H, $OCH_2$), 4.23 (dd, 1H, $OCH_2$), 4.77 (d, 2H, $OCH_2$), 5.26 (s, 1H, CHO), 6.72–7.36 (m, 6H, CH arom.). MS *m/z*: 384 $(C_{21}H_{21}NO_4S+H)^+$.

**5.7.40. *N*-[2-(3-Methoxy-4-prop-2-ynyloxyphenyl)-ethyl]-2-prop-2-ynyloxy-2-pyridin-3-yl-acetamide (75).** Obtained from pyridine-3-carbaldehyde (instead of 4-chloro-benzaldehyde) according to procedures 5.7. and 5.7.1. Yield: 41%. $^1$H NMR ($CDCl_3$): $\delta$ 2.49 (t, 1H, C≡CH), 2.52 (t, 1H, C≡CH), 2.81 (t, 2H, $CH_2CH_2$), 3.53 (q, 2H, $CH_2CH_2$), 3.86 (s, 3H, $OCH_3$), 3.97 (dd, 1H, $CH_2C$≡C), 4.18 (dd, 1H, $CH_2C$≡C), 4.75 (d, 2H, $CH_2C$≡C), 4.94 (s, 1H, CHO), 6.72–7.44 (m, 7H, CH arom.). MS *m/z*: 379 $(C_{22}H_{22}N_2O_4+H)^+$.

**5.8. 2-(4-Chlorophenyl)-*N*-[2-(3-methoxy-4-prop-2-ynyl-oxyphenyl)-ethyl]-2-oxo-acetamide (16)**

A solution of dimethyl sulfoxide (0.98 ml, 13.8 mmol) in 6 ml of dichloromethane was added to a solution of oxalyl chloride (0.92 ml, 10.9 mmol) in 10 ml of dichloromethane at −63 °C in 15 min. A solution of 2-(4-chlorophenyl)-2-hydroxy-*N*-[2-(3-methoxy-4-prop-2-ynyloxyphenyl)-ethyl]-acetamide (**14**, 2.62 g, 7.0 mmol) in 52 ml of dichloromethane was added during 10 min at the same temperature. After 15 min stirring, a solution of triethylamine (3.74 ml, 26.8 mmol) in 8.4 ml of dichloromethane was added during 15 min. After 15 min stirring, the solution was hydrolysed with 12 ml water and warmed up to room temperature. The organic layer was separated, washed with a solution of sodium bisulfite and brine, dried over magnesium sulfate and evaporated. The remainder was purified by chromatography on silica gel (ethyl acetate/hexane, 1:3). Yield: 2.25 g (6.1 mmol, 87%). $^1$H NMR ($CDCl_3$): $\delta$ 2.51 (t, 1H, C≡CH), 2.88 (t, 2H, $CH_2CH_2$), 3.63 (t, 2H, $CH_2CH_2$), 3.89 (s, 3H, $OCH_3$), 4.75 (m, 2H, $CH_2C$≡C), 6.77 (m, 2H, CH arom.), 6.96 (m, 1H, CH arom.), 7.17 (br s, 1H, NH), 7.45 (m, 2H, CH arom.), 8.30 (m, 2H, CH arom.). MS *m/z*: 370 $(C_{20}H_{18}ClNO_4-H)^-$.

**5.9. 2-(4-Chlorophenyl)-2-methoxyimino-*N*-[2-(3-methoxy-4-prop-2-ynyloxyphenyl)-ethyl]-acetamide (15)**

A solution of 2-(4-chlorophenyl)-*N*-[2-(3-methoxy-4-prop-2-ynyloxyphenyl)-ethyl]-2-oxo-acetamide (**16**, 2.2 g, 5.92 mmol), *O*-methyl-hydroxylamine hydrochloride (0.62 g, 7.4 mmol) and pyridine (0.94 ml, 11.6 mmol) in 12 ml of methanol was heated at reflux for 2 h. After evaporation of the solvent, the remainder was purified by chromatography on silica gel (ethyl acetate/hexane, 35:65). Yield: 1.37 g ( 3.4 mmol, 58%). $^1$H NMR ($CDCl_3$): $\delta$ 2.44 (t, 1H, C≡CH), 2.84 (t, 2H, $CH_2CH_2$), 3.71 (q, 2H, $CH_2CH_2$), 3.81 (s, 3H, $OCH_3$), 3.91 (s, 3H, $OCH_3$), 4.76 (m, 2H, $CH_2C$≡C), 6.20 (br s, 1H, NH), 6.72 (m, 2H, CH arom.), 6.97 (m, 1H, CH arom.), 7.32 (m, 2H, CH arom.), 7.50 (m, 2H, CH arom.). MS *m/z*: 445 $(C_{21}H_{21}ClN_2O_4+HCOO)^-$.

**5.10. 2-(4-Chlorophenyl)-2-methylthioimino-*N*-[2-(3-methoxy-4-prop-2-ynyloxyphenyl)-ethyl]-acetamide (17)**

A solution of 2-(4-chloro-phenyl)-*N*-[2-(3-methoxy-4-prop-2-ynyloxyphenyl)-ethyl]-2-oxo-acetamide (**16**, 0.8 g, 2.15 mmol), *N*,*N*-bis(trimethylsilyl)methanesulfenamide (7.0 g, 33.7 mmol) and tetrabutylammonium fluoride trihydrate (250 mg, 0.8 mmol) in 18 ml of tetrahydrofuran was heated at reflux for 2 h. The solution was diluted with ethyl acetate and washed with brine. The organic layer was dried over magnesium sulfate and evaporated. The remainder was purified by chromatography on silica gel (ethyl acetate/hexane, 3:7). Yield: 0.31 g ( 0.74 mmol, 35%). $^1$H NMR ($CDCl_3$): $\delta$ 2.51 (t, 1H, C≡CH), 2.62 (s, 3H, $SCH_3$), 2.84 (t, 2H, $CH_2CH_2$), 3.59 (q, 2H, $CH_2CH_2$), 3.89 (s, 3H, $OCH_3$), 4.77 (m, 2H, $CH_2C$≡C), 6.77 (m, 2H, CH arom.), 6.97 (m, 1H, CH arom.), 7.17 (br s, 1H, NH), 7.51 (m, 4H, CH arom.). MS *m/z*: 417 $(C_{21}H_{21}ClN_2O_3S+H)^+$.

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