Stereoselective Synthesis of a Potent Human NK_1 Receptor Antagonist via Acyl-Claisen Rearrangement

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This work is dedicated to Professor Jerzy Wicha on the occasion of his 70th birthday.

Abstract: Stereoselective synthesis of the tetrahydropyran derivative **1** is reported. Diastereoselective acyl-Claisen rearrangement was employed for formation of C3 and C4 chiral centres on the tetrahydropyran ring.

Key words: acyl-Claisen rearrangement, asymmetric synthesis, total synthesis, stereoselectivity, NK_1 receptors

Neurokinin-1 (NK_1) receptor antagonists are of continuing interest since the natural ligand for the NK_1 receptor – Substance P – has been implicated in the pathophysiology of a wide range of disease conditions including neurogenic inflammation, transmission of pain, emesis and depression.[1,2] Recently, the Merck NK_1 antagonist, aprepitant (Emend®), has been approved for the prevention of acute and delayed chemotherapy-induced nausea and vomiting (Figure 1). Since 1991, when the first non-peptidic antagonist was reported,[3] numerous selective and structurally diverse NK_1 ligands have been identified and subsequently developed.[1,4] Recently, syntheses of *trans*,*trans*-substituted tetrahydropyran derivatives have been described.[4g,h] In the search for selective hNK_1 receptor antagonists, we were interested in examining 3,4,5-*trans*,*trans*-trisubstituted tetrahydropyran derivatives. Compound **1** was identified for synthesis and biological evaluation.

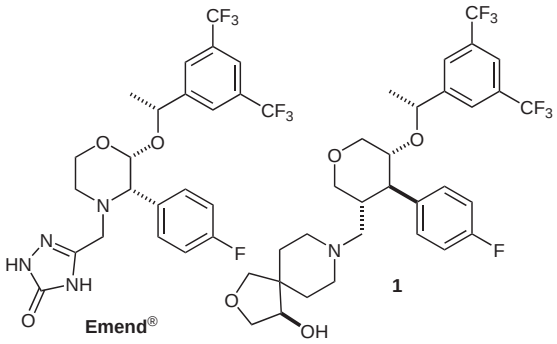
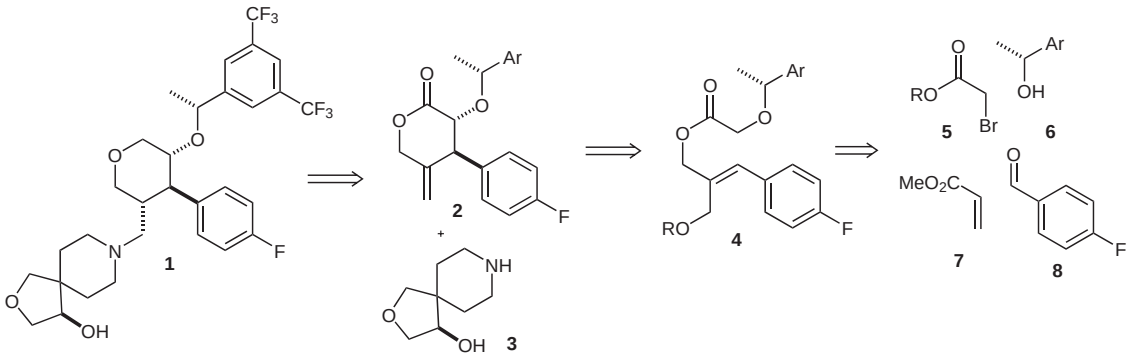


Figure 1

In this communication, we report our approaches to the stereoselective synthesis of a 3,4,5-trisubstituted tetrahydropyran **1**, a potent NK_1 receptor antagonist.

Conceptually, **1** can be disconnected into two fragments, a *trans* lactone **2** and the chiral spiropiperidine **3** (Scheme 1).

We envisaged that the optically pure *trans* lactone **2** would be accessible from the chiral allyl ester **4** through the diastereoselective Ireland–Clasien rearrangement[5] and subsequent lactonisation of the resulting hydroxy acid. In turn, **4** could be assembled from commercially



Scheme 1 Ar = 3,5-bis(trifluoromethyl)phenyl

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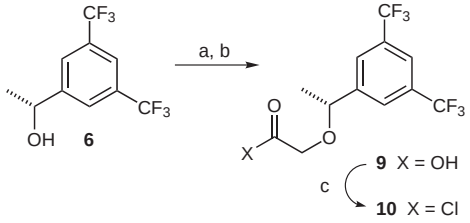
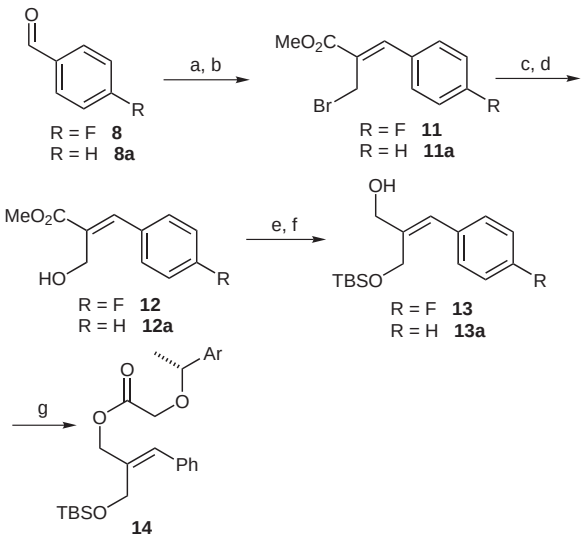


Scheme 2 *Reagents and conditions*: a) *tert*-butyl bromoacetate, NaH, THF, 90%; b) TFA, CH_2Cl_2, 56%; c) $(COCl)_2$, CH_2Cl_2, cat. DMF, quant.

available compounds: bromoacetate **5**, (*R*)-1-[3,5-bis(trifluoromethyl)phenyl]ethanol (**6**), methyl acrylate (**7**) and 4-fluorobenzaldehyde (**8**).

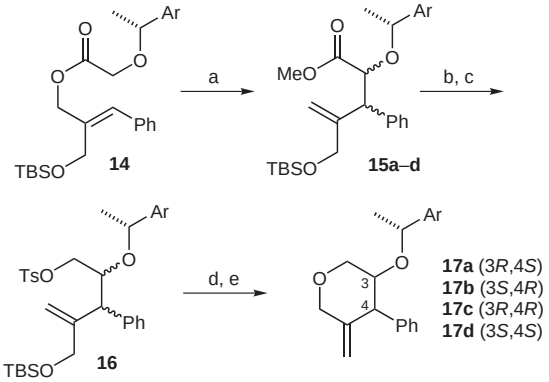
Chiral alcohol **6** was chosen as a starting nonracemic building block. We assumed that the chiral benzylic centre might be a stereocontrolling element in the [3+3] sigmatropic rearrangement and would facilitate definition of stereochemistry of new chiral centres on the tetrahydropyran ring.

The synthesis started with alkylation of the commercially available *R* alcohol **6** with *tert*-butyl bromoacetate followed by removal of the *tert*-butyl group providing the acid **9** in 50% overall yield (Scheme 2).



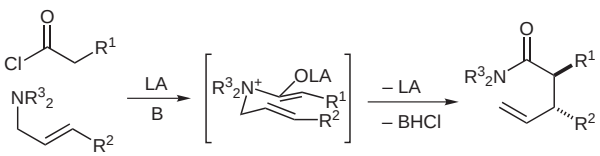
Scheme 3 *Reagents and conditions*: a) methyl acrylate, DABCO, 60 °C, 66–70%; b) PBr_3, Et_2O, 0 °C to r.t.; c) Et_3N, HCO_2H, MeCN, reflux; d) concd HCl, MeOH, 62–70% (3 steps); e) TBSCl, DMF, imidazole, quant.; f) DIBAL-H, CH_2Cl_2, 86%; g) **13a**, **9**, EDC, Et_3N, DMAP, CH_2Cl_2, 86%. Ar = 3,5-bis(trifluoromethyl)phenyl.

Having prepared the acid **9**, our next problem was selective preparation of *Z*-allyl alcohols **13** and **13a** (Scheme 3). This was accomplished by a six-step sequence beginning with the Baylis–Hillman reaction of methyl acrylate and corresponding benzaldehyde (**8**, **8a**) followed by treatment with PBr_3 in diethyl ether to afford allyl bromides **11** and **11a**.[6] Displacement of bromine in **11** and **11a** with formate and hydrolysis of the resulting formic acid ester gave allylic alcohols **12** and **12a** in 40–50% overall yields.[6] The hydroxy group in **12** and **12a** was protected as a *tert*-butyldimethylsilyl ether and the ester reduced using DIBAL-H to give *Z*-allylic alcohols **13** and **13a** in 86% yield. Finally, the standard coupling of the alcohol **13a** with the acid **9** provided the allylic ester **14** in 86% yield. The Ireland–Claisen rearrangement of the lithium enolate of **14** in the presence of trimethylsilyl chloride yielded a mixture of isomeric acids that were converted to methyl esters on treatment with trimethylsilyldiazomethane (Scheme 4). ^{1}H NMR analysis of the crude mixture of esters indicated the diastereoisomeric ratio of mixture **15a**:**15b**:**15c**:**15d** = 2:10:1:2. To establish relative stereochemistry of products of the rearrangement, the mixture of esters **15a**–**d** was converted into a mixture of tetrahydropyrans **17a**–**d** as outlined in Scheme 4. Isomers were separated and the relative stereochemistry of diastereoisomers was assigned by ^{1}H NMR/NOE experiments. Disappointingly, we found that the undesired *trans* isomer, **17b**, was a major product of this sequence.



Scheme 4 *Reagents and conditions*: a) LiHMDS, TMSCl, THF, then TMS–diazomethane, Et_2O, MeOH, 65%; b) DIBAL-H, CH_2Cl_2, 77%; c) TsCl, Et_3N, DMAP, CH_2Cl_2, 90%; d) TBAF, THF; e) BuLi, THF, 64% (two steps). Ar = 3,5-bis(trifluoromethyl)phenyl.

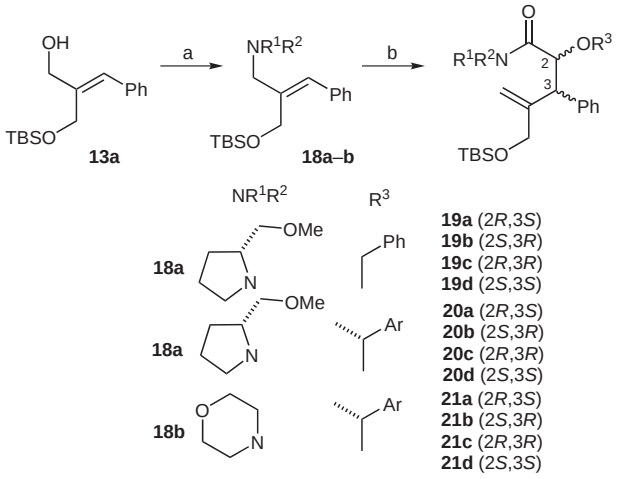
To overcome this obstacle, we turned our attention towards the acyl-Claisen rearrangement.[7] Recently, MacMillan and co-workers reported an enantioselective Lewis acid catalysed acyl-Claisen rearrangement of allylic amines and ketenes (Scheme 5).[8] Ketenes were generated in situ from corresponding acyl chlorides.



Scheme 5

We have hypothesised that having a chiral centre on the allylic amine might invert stereoselectivity in the sigmatropic rearrangement. With the allylic alcohol **13a** in hand, we were in a position to test this hypothesis and briefly investigate this substrate control in the acyl-Claisen reaction.

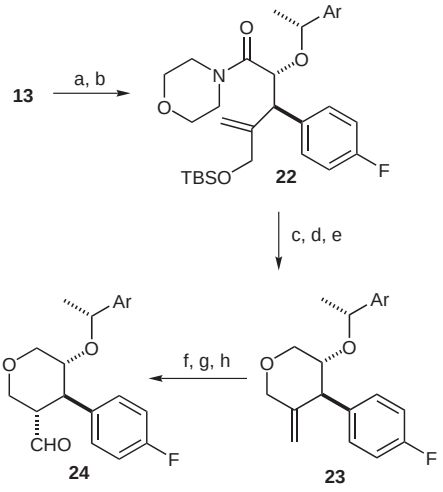
We began with the synthesis of allyl amines **18a** and **18b** (Scheme 6). For our studies, we selected (*R*)-*O*-methylprolinol as a chiral amine and morpholine as an achiral analogue. Thus, treatment of the alcohol **13a** with methanesulphonyl chloride followed by the corresponding amine afforded **18a**[9] and **18b** in 61–67% yield. Reaction of the allyl amine **18a** and benzyloxyacetyl chloride in the presence of *i*-Pr_2EtN and catalytic $TiCl_4$–THF_2 yielded a mixture of two major *syn* diastereoisomers in the ratio **19a**:**19b** = 1:1. Pleasingly, reaction of the chiral acid chloride **10** and **18a** proceeded smoothly to give a mixture of four diastereoisomers **20a**–**d** in the ratio **20a**:**20b**:**20c**:**20d** = 18:3:5:2 with the major *syn* diastereoisomer **20a**[10] having the correct stereochemistry at C2 and C3 centres.[11] Reaction of the morpholine **18b** with **10** furnished with a mixture of four morpholine amides **21a**–**d** in the ratio **21a**:**21b**:**21c**:**21d** = 4.2:3:1:1 showing that both chiral centres are required for selectivity.



Scheme 6 *Reagents and conditions*: a) MsCl, Et_3N, CH_2Cl_2, 0 °C, then R^1R^2NH, 61–67%; b) $BnOCH_2COCl$ or **10**, cat. $TiCl_4$–THF_2, *i*-Pr_2EtN, CH_2Cl_2, –10 °C to 10 °C (58% for **20a**). Ar = 3,5-bis(trifluoromethyl)phenyl.

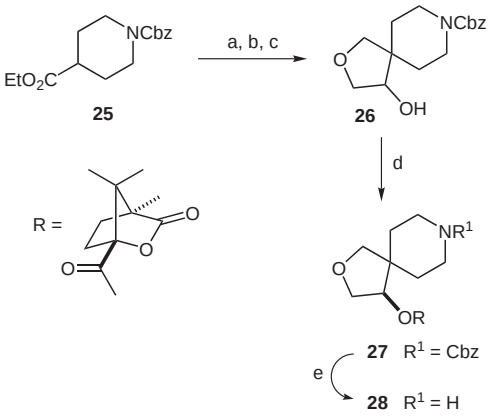
The morpholine amide **22** was prepared from the alcohol **13** in a similar way as described for **21a** (Scheme 7). Acid-catalysed TBS-group deprotection–lactonisation on the amide **22** followed by reduction to the corresponding lactol using DIBAL-H gave a mixture of lactols which were reduced to the tetrahydropyran **23** using triethylsilane in the presence of boron trifluoride–diethyl ether complex. Hydroboration–oxidation of the double bond in **23** furnished a 2:1 mixture of hydroxymethyl epimers in favour of the undesired 5*R* epimer. This mixture was oxidised to the aldehyde under Swern conditions and the mixture of aldehydes was allowed to equlibrate in the presence of catalytic 1,8-diazabicyclo[5.4.0]undec-1-ene (DBU) in dichloromethane providing the required 5*S* aldehyde **24** (de 94% by ^1H NMR) in 81% yield.

Spirocyclic piperidine **27** was prepared starting from ethyl isonipecotate **25** (Scheme 8). Aldol condensation of the lithium enolate of **25** with (*tert*-butyldimethylsilyloxy)acetaldehyde followed by reduction of the diester



Scheme 7 *Reagents and conditions*: a) MsCl, Et_3N, CH_2Cl_2, 0 °C, then morpholine, 64%; b) **10**, cat. $TiCl_4$–THF_2, *i*-Pr_2EtN, CH_2Cl_2, –70 °C to r.t., 27%; c) *p*-TSA, MeOH, PhMe, 71%; d) DIBAL-H, CH_2Cl_2, –78 °C, quant.; e) Et_3SiH, $BF_3{\cdot}OEt_2$, CH_2Cl_2, 93%; f) $BH_3{\cdot}THF$, –78 °C to r.t.; then H_2O_2, NaOH, 81%; g) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, –60 °C to 0 °C; h) DBU (cat.), CH_2Cl_2, 99% (two steps). Ar = 3,5-bis(trifluoromethyl)phenyl.

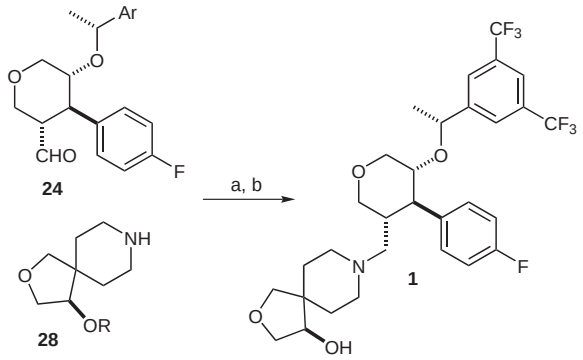
using lithium borohydride, removal of the TBS group with tetrabutylammonium fluoride and subsequent cycloetherification of the resulting triol under Mitsunobu conditions afforded the racemic alcohol **26** in 44% overall yield.



Scheme 8 *Reagents and conditions*: a) $TBSOCH_2CHO$, LiHMDS, THF, 76%; b) $LiBH_4$, THF; then TBAF, THF, 76%; c) DEAD, Ph_3P, THF, 76%; d) RCl, Et_3N, DMAP, CH_2Cl_2, 38%, de 98%; e) Pd/C, H_2, TFA, EtOH, quant.

Acylation of **26** with (–)-camphanic acid chloride and subsequent crystallisation of the mixture of diasteroisomeric esters from methanol–water gave the ester **27** as a white solid (38% yield, de 98%).[12] Removal of the benzyl carbamate provided the spirocyclic piperidine **28** in quantitative yield.

Finally, reductive amination of the aldehyde **24** with piperidine **28** and sodium triacetoxyborohydride followed by saponification of the camphanate ester furnished **1**[13] in



Scheme 9 *Reagents and conditions*: a) $NaHB(OAc)_3$, DCE; b) NaOH, MeOH–H_2O, 50%. Ar = 3,5-bis(trifluoromethyl)phenyl.

50% yield (Scheme 9). The tetrahydropyran **1** was tested in the NK_1 receptor binding affinity assay in vitro[14] and it was found to antagonise the human NK_1 receptor with IC_{50} = 0.15 nM.

In conclusion, the stereoselective synthesis of novel NK_1 antagonist based upon the tetrahydropyran framework was developed. Diastereoselectivity in the acyl-Claisen sigmatropic rearrangement of **18a**,**b** and **10** was investigated allowing inversion of the distereoselective outcome of Ireland–Claisen rearrangement of **14**. The synthesis of tetrahydropyran **1** was accomplished and the binding affinity of **1** at the human NK_1 receptor was determined. The tetrahydropyran derivative **1** exhibited excellent binding affinity at the human NK_1 (IC_{50} 0.15 nM).

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(9) **Experimental Procedure for the Preparation of 18a.** Methanesulphonyl chloride (0.12 mL, 1.5 mmol) was added dropwise to an ice-bath-cooled, stirring mixture of **13a** (280 mg, 1 mmol), Et_3N (0.4 mL, 2.8 mmol) and CH_2Cl_2 (2 mL). The mixture was stirred for 90 min and (*R*)-2-(methoxymethyl)pyrrolidine (0.2 mL, 1.6 mmol) was added. The mixture was stirred for 2 h and poured onto a sat. aq solution of $NaHCO_3$. The mixture was extracted into CH_2Cl_2. The organic extract was dried (Na_2SO_4) and concentrated. The residue was purified on silica gel (CH_2Cl_2–2 M NH_3 in MeOH, 0–10%) to give the amine **18a** (230 mg, 61%). ^1H NMR (360 MHz, $CDCl_3$): δ = 0.04 (6 H, s), 0.90 (9 H, s), 1.61–1.77 (3 H, m), 1.86–2.01 (1 H, m), 2.21 (1 H, q, *J* = 8.5 Hz), 2.67 (1 H, m), 2.95 (1 H, d, *J* = 13.2 Hz), 3.04 (1 H, m), 3.25 (1 H, dd, *J* = 7.4, 9.1 Hz), 3.35 (3 H, s), 3.46 (1 H, dd, *J* = 4.5, 9.3 Hz), 3.74 (1 H, d, *J* = 13.1 Hz), 4.26 (2 H, s), 6.58 (1 H, s), 7.29–7.31 (5 H, m).

(10) **Experimental Procedure for the Preparation of 20a.** $TiCl_4$–THF_2 (33 mg, 0.1 mmol) was added to a stirred mixture of **18a** (375 mg, 1 mmol), *i*-Pr_2EtN (0.3 mL, 1.7 mmol) at –10 °C followed by **10** (510 mg, 1.5 mmol). The mixture was stirred at –10 °C for 30 min and warmed to 10 °C over 1 h. The mixture was treated with 1 M aq NaOH and the mixture was extracted into CH_2Cl_2. The organic extract was dried (Na_2SO_4) and concentrated. The residue (a mixture of **20a**:**20b**:**20c**:**20d** in the ratio 18:3:5:2) was purified on silica gel (*i*-hexane–EtOAc, 5–35%) to give the amide **20a** (390 mg, 58%, 5:1 mixture of rotamers). ^1H NMR (400 MHz, $CDCl_3$, a major rotamer): δ = –0.07 (3 H, s), –0.06 (3 H, s), 0.83 (9 H, s), 1.31 (3 H, d, *J* = 6.4 Hz), 1.64–2.00 (4 H, m), 3.26 (1 H, m), 3.29 (3 H, s), 3.33 (1 H, dd, *J* = 6.5, 9.3 Hz), 3.52 (1 H, m), 3.83–3.97 (3 H, m), 4.20 (1 H, m), 4.36 (1 H, d, *J* = 9.3 Hz), 4.55 (1 H, q, *J* = 6.6 Hz), 4.97 (1 H, s), 5.15 (1 H, s), 7.20–7.26 (5 H, m), 7.44 (2 H, s), 7.74 (1 H, s).

(11) Diastereomeric products of the acyl-Claisen reaction were separable by flash chromatography and converted into the corresponding lactones **17a**–**d** as outlined in Scheme 4.

(12) Diasteromeric excess was determined by HPLC analysis. The absolute stereochemistry of C3 centre of tetrahydrofuran ring was determined by X-ray analysis of close analogue of **1**.

(13) **Experimental Procedure for the Preparation of 1.** Sodium triacetoxyborohydride (91 mg, 0.43 mmol) was added to a stirred mixture of **24** (100 mg, 0.215 mmol) and **28** (73 mg, 0.216 mmol) and DCE (0.5 mL). The mixture was stirred for 60 min and treated with a sat. aq solution of $NaHCO_3$ and extracted with CH_2Cl_2. The organic extract was dried (Na_2SO_4) and concentrated. The mixture was treated with MeOH (2 mL) and 4 M aq NaOH (0.3 mL) was added dropwise. The mixture was stirred for 15 min, diluted with H_2O and extracted into CH_2Cl_2. The organic extract was dried (Na_2SO_4) and concentrated. The residue was purified on silica gel (CH_2Cl_2–MeOH, 0–10%) to give **1** (66 mg, 50%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.30 (3 H, d, *J* = 6.4 Hz), 1.38–1.50 (3 H, m), 1.77 (1 H, dd, *J* = 3.0, 12.5 Hz), 1.81 (1 H, m), 1.97 (1 H, t, *J* = 10.7 Hz), 2.01–2.11 (2 H, m), 2.12–2.20 (1 H, m), 2.30 (1 H, t, *J* = 10.6 Hz), 2.40 (1 H, m), 3.12 (1 H, t, *J* = 11.5 Hz), 3.25 (1 H, t, *J* = 10.8 Hz), 3.42 (1 H, dt, *J* = 4.7, 9.8 Hz), 3.52 (1 H, AB, *J* = 8.6 Hz), 3.57 (1 H, AB, *J* = 8.6 Hz), 3.64 (1 H, dd, *J* = 2.2, 10.1 Hz), 3.88 (1 H, m), 4.01 (1 H, dd, *J* = 4.6, 10.1 Hz), 4.21 (1 H, dd, *J* = 4.5, 11.8 Hz), 4.25 (1 H, dd, *J* = 4.6, 11.0 Hz), 4.27 (1 H, q, *J* = 6.5 Hz), 6.83 (2 H, t, *J* = 8.9 Hz), 6.93 (2 H, m), 7.20 (2 H, s), 7.66 (1 H, s).

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