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Design, synthesis and conformational analysis of turn inducer cyclopropane scaffolds: microwave assisted amidation of unactivated esters on catalytic solid support to obtain γ-turn mimic scaffolds

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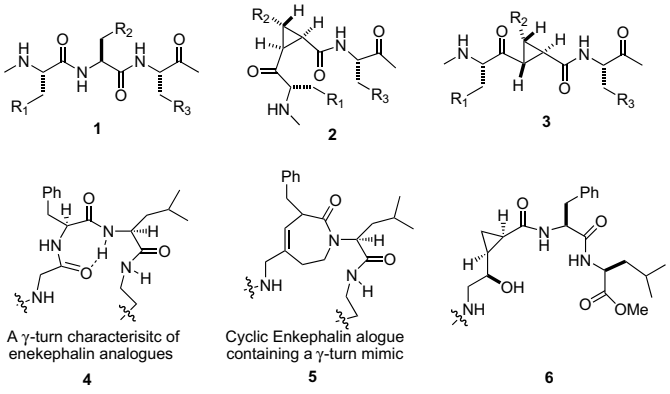
ABSTRACT

Novel constrained 1-aroyl-cyclopropane-2,3-*cis*-dicarboxylic acid bis-[(2-hydroxy-ethyl)-amides] (**17a–e**) with varied torsional angles have been synthesized in high yield from unactivated esters of 1-aroyl-2,3-*cis*-diethoxycarbonylcyclopropanes (**15a–e**) on a catalytic solid support with reduced reaction times by using the monomode-microwave irradiation; **15a–e** were obtained by diastereoselective ethoxycarbonylmethylene transfer from a sulfur ylide to ethyl β-aroylacrylates (**10a–e**). Torsional angles and interatomic distance measurements on the energy minimized structures of the obtained molecules (**17a–e**, DFT, B3LYP/6-31G* level) have established these molecules as valuable γ-turn mimic scaffolds.

1. Introduction

Cyclopropane derivatives are interesting structural scaffolds, which have attracted considerable attention as rigid replacement for a dipeptide array and have been employed as dipeptide mimic to obtain biologically active oligopeptides.[1] Martin et al.[2] based on molecular modeling studies suggested that substituted cyclopropanes serve as novel, rigid replacements of peptide (**1**). The cis-relationship of substituents on cyclopropane (**2**) is envisioned to induce a turn and the alternative trans-arrangement of the backbone substituents on cyclopropane (**3**) is shown to locally stabilize a β-strand conformation. Structural and computational investigations have revealed that a turn motif is a structural element in the biologically active conformation of enkephalins (**4**) for opioid receptors,[3] and the analogues of enkephalins, such as **5**, have been synthesized having γ-turn motif as a structural element.[4] Consequently, cis-substituted cyclopropanes have been synthesized and utilized to develop enkephalin analogue (**6**).[5]



1 2 3 4 5 6

Recently, the microwave assisted amide bond formation has attracted considerable attention. In several cases, the microwave irradiation has been a successful alternative to the conventional high temperatures for direct condensation of amines to carboxylic acids without prior activation.[6] The microwave irradiation may be run with or without a catalyst.[7] Different kinds of catalysts such as K-10 montmorillonite, imidazole, zeolite-HY, polyphosphoric acid, *p*-toluenesulfonic acids, $TaCl_5$–silica gel, KF–alumina and silica gel

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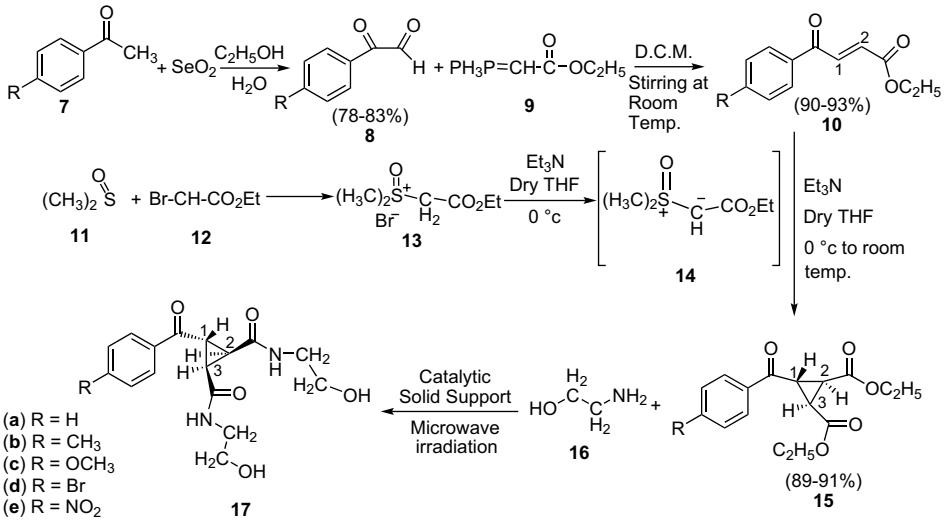


Scheme 1.

have been employed.[8] The transformation of the aromatic esters to the amide by reacting with amines under microwave irradiation has also been reported over the neutral alumina.[8h]

Herein, we report the design, synthesis and DFT analysis of the turn inducer cyclopropane scaffolds, i.e., 1-aroyl-2,3-*cis*-dicarboxylic acid bis-[(2-hydroxy-ethyl)-amide], as useful precursors to enkephalin mimicking ligands for opioid receptor. The amides were derived from the 1-aroyl-2,3-*cis*-diethoxycarbonylcyclopropanes by amidation of the ethoxycarbonyl functions employing focused monomode-microwave irradiation of reactants on solid support.

2. Result and discussion

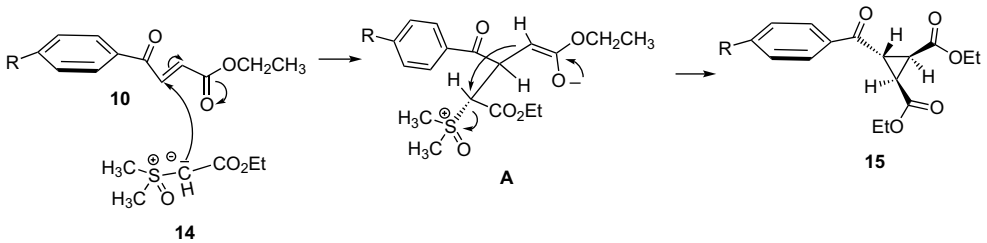
The *p*-substituted acetophenones (**7a**–**e**) were converted to *p*-substituted phenylglyoxals (**8a**–**e**) by oxidation with SeO_2 in ethanol–water mixture (Scheme 1).[9a] Conversions of the *p*-substituted phenylglyoxals (**8a**–**e**) into the ethyl β-aroylacrylates (**10a**–**e**) was achieved by their Wittig reaction with ethoxycarbonylmethyledine-triphenylphosphorane (**9**) in dry dichloromethane at room temperature (Scheme 1). After column chromatographic purification, the ethyl β-aroylacrylates (**10a**–**e**) were isolated in high yields and characterized spectroscopically.

Diastereoselective ethoxycarbonylmethylene transfer from a sulfur ylide (**14**) to ethyl β-aroylacrylates (**10a**–**e**)[9b] afforded 3-aroyl-2,3-*cis*-diethoxycarbonylcyclopropanes (**15a**–**e**); the sulfur ylide (**14**) was generated in situ from dimethyl-ethoxycarbonlymethyl-oxosulfonium bromide (**13**)[9] in the presence of triethylamine under nitrogen environment, in dry tetrahydrofuran (Scheme 1). The cyclopropanes (**15a**–**e**) were obtained in high yields (89–90%) after column chromatographic purification. The present approach involving sulfur ylides is less cumbersome and is attended with high yields as compared to the reported 1,2,3-trisubstituted cyclopropane syntheses.[10]

Structures of compounds **15a**–**e** were established by detailed spectroscopic analysis. For instance, **15a** in its ^{1}H NMR spectrum revealed a 1H triplet at δ 3.75 (J=5.6 Hz, C1–*H*) and a 2H doublet at δ 2.71 (J=5.6 Hz, C2–*H* and C3–*H*). In the ^{13}C NMR spectrum of **15a** the resonances of the C2,3 appeared at δ 30.0 and of C1 at δ 28.9. The obtained ^{1}H and ^{13}C NMR spectral data clearly indicated a cis-arrangement at C2 and C3 between ester functions and the observed coupling constant value of C2–H/C3–H with C1–H was characteristic of a trans-arrangement.[11] The structures of compounds **15a**–**e** were also corroborated by the IR and mass (ESI) spectroscopic data.

Mechanistically, the diastereoselective formation of 1-aroyl-2,3-*cis*-diethoxycarbonylcyclopropanes (**15a**–**e**) can be rationalized in terms of attack of sulfur ylide on the aroyl-substituted carbon of acrylates leading to intermediate **A**, wherein the ester of the ylide and aroyl moiety is placed trans to each other, and there is complete retention of the configurations of the acrylates giving rise to the most stable trans product with respect to the benzoyl moiety and cis product with respect to the ethoxycarbonyl moiety of the acrylate (**10**, Scheme 2). The retention of the configuration in case of similar additions to acrylates during the formation of cyclopropanes is precedented.[11]

The conversion of ester functionalities of 1-aroyl-2,3-diethoxycarbonylcyclopropanes (**15a**–**e**) into amides (**17a**–**e**) with the primary amine (**16**) was investigated under microwave irradiation using a focused monomode-microwave reactor (CEM-Discover). Different types of solid supports viz. silica gel G, neutral alumina and montmorillonite KSF were used to convert esters (**15a**–**e**) into amides (**17a**–**e**); the results are summarized in Scheme 1 and Table 1.



Scheme 2.

Table 1
Yields[a] of amides (**17a–e**) with different solid supports under monomode-microwave irradiation

Entry	Silica gel G[b] (t_R=8 min)	Neutral alumina[c] (t_R=5 min)	Montmorillonite KSF[c] (t_R=3 min)
17a	32% (114 mg)	75% (267 mg)	96% (342 mg)
17b	35% (124 mg)	75% (266 mg)	97% (344 mg)
17c	30% (105 mg)	73% (257 mg)	95% (334 mg)
17d	35% (121 mg)	75% (259 mg)	96% (332 mg)
17e	32% (113 mg)	75% (265 mg)	96% (340 mg)

t_R=reaction time.
[a] Yield refers to isolated pure product.
[b] Power 250 W, temp 198 °C.
[c] Power 150 W, temp 121 °C.

In the case of the montmorillonite KSF, almost optimal conversion of ester to the amide bond was observed. This conversion of the ester to the amide bond under focused monomode-microwave irradiation required very short reaction time and is also cost effective as compared to the reported conventional method involving use of metal alkoxides in conjunction with the additives such as 1-hydroxy-7-azabenzotriazole (HOAT).[12]

The products **17a–e** were characterized by rigorous spectroscopic analysis. The conversion of the ester functionalities of **15a–e** to the amide bonds (**17a–e**) was clearly reflected in the IR spectral data. For instance, in the case of **17d**, a sharp band appeared at 1649 cm^{-1} in the IR spectrum due to the amide carbonyl groups and erstwhile ester carbonyl band observed in the IR spectrum of **15d** disappeared; another sharp band appeared at 1670 cm^{-1} due to the carbonyl group of aroyl moiety. The N–H and O–H stretchings appeared in the range 3423–3314 cm^{-1} as multiple bands. In the ^1H NMR spectrum of **17d** the resonance for the two N*H*s was observed as a broad signal at δ 7.86, and the broad resonance of the two O*H*s appeared at δ 2.59 (both were suppressed on deuterium exchange). A multiplet (4H) of two OH linked methylenes (2×CH_2) appeared at δ 3.70–3.56 and protons of two NH linked methylenes (2×C*H*$_2$–NH) appeared as two multiplets (2H each) at δ 3.48–3.31 and δ 3.30–3.22. These changes in the ^1H NMR spectrum, i.e., appearance of new resonance and disappearance of the resonances of the erstwhile ethyl moiety of **15d** clearly established the structure of amide **17d**. The protons of the cyclopropane moiety in **17d** appeared as a triplet at δ 3.79 (J=5.4 Hz, C1–*H*) and as a doublet (2H) at δ 2.67 (J=5.4 Hz, C2–H and C3–H). In the ^{13}C NMR spectrum of **17d** the resonance of ketone carbonyl carbon showed up at δ 195.4 and the amide carbonyls appeared at δ 167.7. The C2,3 were located at δ 32.1 and C1 at δ 28.0. The obtained ^1H and ^{13}C NMR spectral features of the cyclopropane moiety again indicated the retention of cis-arrangement of the amide chains. The formation of **17a–e** was also corroborated by the mass spectroscopy; the mass (ESI) spectrum of **17d** revealed the $(M+Na)^+$ peak at 421.0. Attempts to develop the crystal for X-ray crystallographic structure determination have not succeeded as yet.

Table 2
Important dihedral angles, hydrogen bond angles and hydrogen bond lengths calculated at B3LYP/6-31G* level for compounds **17a–e**

Atoms	17a	17b	17c	17d	17e
C(25)–C(22)–C(23)–C(26) (dihedral angles)	−8.4°	−8.0°	−8.2°	−8.6°	−9.2°
C(25)–C(22)–C(24)–C(2) (dihedral angles)	−136.5°	134.5°	135.6°	136.0°	137.5°
C(26)–C(23)–C(24)–C(2) (dihedral angles)	130.9°	130.4°	130.6°	130.3°	129.7°
C═O···H–N (H-bond angles)	149.2°	151.2°	150.9°	149.6°	148.8°
N–H···O═C (H-bonding lengths)	1.919 Å	1.893 Å	1.901 Å	1.910 Å	1.920 Å

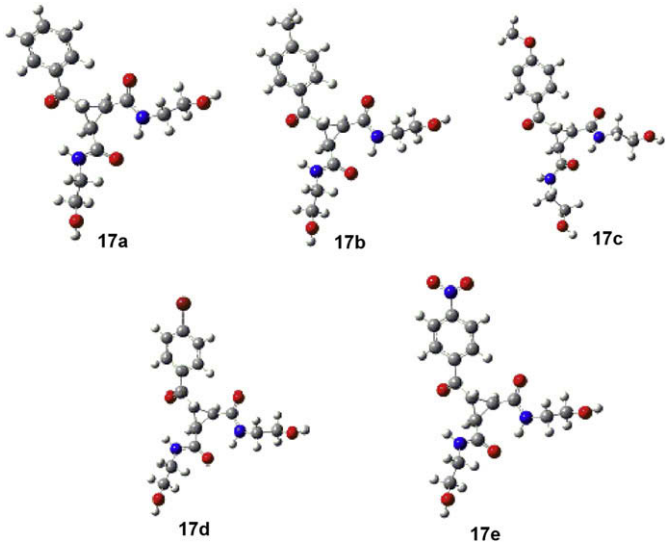


Figure 1. Optimized geometrical structures of **17a–e** calculated at the B3LYP/6-31G* level.

2.1. The density functional theory (DFT) analysis

Since, the cyclopropane ring in **17a–e** exhibits a certain 'unsaturated character', which results in restriction of the torsion angles about the C_α–C═O bond to small values, due to conjugation of the carbonyl group with the ring, resulting in marked restriction of the conformational space to torsional angles between 0° and ±90°, thereby, leading to observed turn conformation.[13] For conformational studies, various dihedral angles for **17a–e** were measured by DFT analysis (Table 2). All the data were taken from the completely optimized structure of the respective molecules at B3LYP/6-31G* level of calculation (Fig. 1).

In the case of **17a**, the dihedral angle involving C(25)–C(22)–C(23)–C(26) is −8.4°, which is in the synperiplanar range corresponding to the cis-arrangement of amide chains attached at the C2 and C3 carbons of the cyclopropane ring and hence the turn motif, whereas the dihedral angles between C(25)–C(22)–C(24)–C(2) and C(26)–C(23)–C(24)–C(2) were 136.5° and −130.9°, respectively, corresponding to the *anti* or trans conformation (Fig. 2).[14] The reported theoretical and computational calculations[14b] on the minimum energy conformations on polypeptides have revealed that H-bonding (hydrogen bonding) exists between the N–H···O═C of the backbone peptide bonds if the distance between N–H···O═C is 1.8–2.9 Å. These H-bonding patterns are responsible for stabilizing the turn conformations in the peptide chains.[14b] For **17a–e**, the N–H···O═C distance of the two adjacent amide function is 1.919, 1.893, 1.901, 1.910 and 1.920 Å, respectively, as calculated from completely optimized structure of the respective molecules at B3LYP/6-31G* level (Fig. 1 and Table 2); this range of distances is characteristic for the H-bonding between the C═O···H–N of (i) and (i+2) residues of the two adjacent amide chains attached at the C2 and C3 carbons of the cyclopropane ring in **17a–e** to form the seven-membered ring or a γ-turn (Fig. 3). The obtained restricted angle distribution qualifies these compounds (**17a–e**) as peptide mimics, which requires the restriction of the angles φ (phi), ψ (psi) and ω (omega), which determine the 3D structure of the peptide backbone,[15] as well as the χ (chi) torsional angles that define the position of the side chain functional groups.[15d]

3. Conclusions

The direct transformation of diastereoselectively synthesized unactivated ester functionalities of **15a–e** into amides (**17a–e**) over

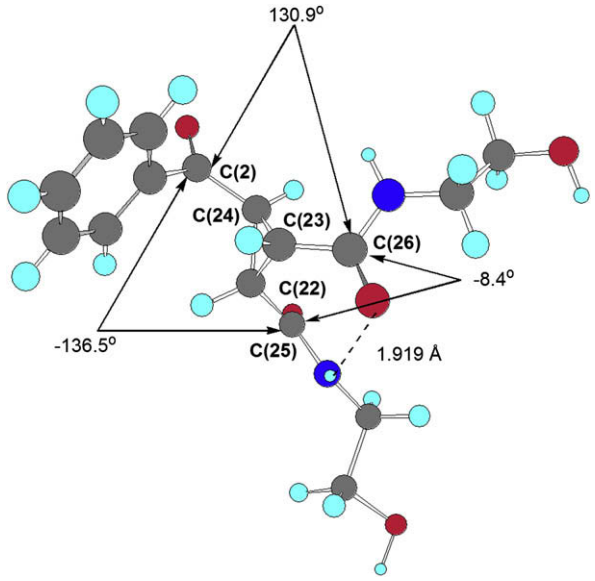


Figure 2. Diagrammatic representation of **17a** showing N–H···O=C distance and dihedral angles.

montmorillonite KSF under microwave irradiation is potentially a valuable process for their incorporation into polypeptides. The present approach involving sulfur ylides is less cumbersome and is attended with high yields as compared to the reported 1,2,3-trisubstituted cyclopropane syntheses.[10] The DFT analysis of **17a–e** has revealed that the cyclopropane ring with cis-arrangement of the amide chains attached to the cyclopropane ring induces a γ-turn conformation while projecting the amino acid side chains in orientations approximating selected χ angles, which could serve as valuable precursors to peptidomimetics of enkephalin ligands for opioid receptors as well as other polypeptides possessing such γ-turn motifs.[16a] These cyclopropane scaffolds (**17a–e**) can be exploited as photo-switch through the cis–trans photo-isomerization;[16b] it is anticipated that the trans-arrangement shall lead to an extended conformation of peptide chains.

4. Experimental

4.1. General information

Starting materials and reagents were purchased from commercial suppliers and used after further purification (crystallization/distillation). Bruker AC-200FT (200 MHz) and JEOL AL-300FT (300 MHz) spectrometers were used to record ^{1}H and ^{13}C (50 and 75 MHz) NMR spectra. Chemical shifts (δ) are reported as downfield displacements from TMS that is used as internal standard and coupling constants (J) are reported in hertz. IR spectra were recorded with Shimadzu DR-2001 FT-IR spectrophotometer on KBr pellets. Mass spectra, ESI method, were recorded on Bruker Daltonics Esquire 300 mass spectrometers. The CEM-Discover Focused Monomode-Microwave apparatus (2450 MHz, 300w) was used for microwave irradiation. CHN analysis was performed on thermoelectron CHN analyser EA1112 at Department of Chemistry, Guru Nanak Dev University, Amritsar. All melting points are uncorrected and measured in open glass capillaries on a Veego MP-D digital melting point apparatus. The molecules have been optimized at the B3LYP/6-31G* level. All of them were found to be minimum on the potential energy surface with zero imaginary frequency.

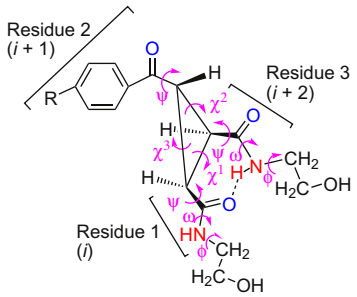


Figure 3. Showing γ-turn and different torsional angles in compounds **17a–e**.

4.2. General procedure for the synthesis of *p*-substituted phenylglyoxals (8a–e) from *p*-substituted acetophenones (7a–e)

In 500 ml round bottom flask were added SeO_2 (18 g), ethanol (100 ml) and water (4 ml), and fitted it with condenser. The mixture was heated to 50–55 °C and stirred until the solid dissolved. It was followed by addition of *p*-substituted acetophenones (**7a–e**, 1.0 mol equiv), respectively, and refluxing of the mixture with stirring was continued. The colour of the solution becomes orange, which instantly changed to red and then to deep red within half an hour. After about 2 h the solution becomes clear and little further precipitation of selenium was observed. The solution was further refluxed for 6 h and the completion of the reaction was monitored by TLC. The hot solution was decanted from the precipitated selenium and filtered through a fluted filter paper. Solvent from filtrate was removed under vacuum and the residual *p*-substituted phenylglyoxal (**8**) was distilled under reduced pressure and collected the fraction boiling at 95–97 °C. The yields of pure *p*-substituted phenylglyoxals (**8**, a yellow liquid) were obtained in 78–83% yields.

4.2.1. *Phenylglyoxal (**8a**)*

Yellow oil; yield 82%; R_f ($CHCl_3$) 0.35; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 9.8 (s, 1H, O=C–*H*), 8.12 (dd, 2H, J=8.5 and 1.4 Hz, arom. Hs), 7.59–7.47 (m, 3H, arom. Hs); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 190.2 (C=O), 187.3 (C=O), 136.7 (q), 135.7 (CH), 134.5 (CH), 129.9 (2CH), 129.2 (2CH); Mass (ESI): 157.0 $(M+Na)^+$.

4.2.2. *p-Tolyl-phenylglyoxal (**8b**)*

Yellow oil; yield 79%; R_f ($CHCl_3$) 0.35; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 9.8 (s, 1H, O=C–*H*), 7.96 (d, 2H, J=7.6 Hz, arom. Hs), 7.17 (d, 2H, J=7.4 Hz, arom. Hs), 2.39 (S, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 190.4 (C=O), 186.9 (C=O), 143.6 (C), 133.5 (q), 129.7 (2CH), 129.5 (2CH), 20.9 (CH_3); Mass (ESI): 171.1 $(M+Na)^+$.

4.2.3. *p-Methoxy-phenylglyoxal (**8c**)*

Yellow oil; yield 83%; R_f ($CHCl_3$) 0.36; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 9.7 (s, 1H, O=C–*H*), 7.98 (d, 2H, J=8.5 Hz, arom. Hs), 6.97 (d, 2H, J=8.5 Hz, arom. Hs), 3.78 (s, 3H, OCH_3); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 190.3 (C=O), 187.1 (C=O), 167.8 (C), 130.9 (2CH), 129.2 (q), 114.6 (2CH), 56.0 (CH_3); Mass (ESI): 187.0 $(M+Na)^+$.

4.2.4. *p-Bromo-phenylglyoxal (**8d**)*

Yellow oil; yield 78%; R_f ($CHCl_3$) 0.34; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 9.8 (s, 1H, O=C–*H*), 7.95 (d, 2H, J=8.7 Hz, arom. Hs), 7.62 (d, 2H, J=8.6 Hz, arom. Hs); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 190.2 (C=O), 187.0 (C=O), 135.7 (q), 132.1 (2CH), 131.9 (2CH), 128.7 (C); Mass (ESI): 235.0 $(M+Na)^+$.

4.2.5. *p-Nitro-phenylglyoxal (**8e**)*

Yellow oil; yield 82%; *Rf* 0.35 ($CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 9.6 (s, 1H, O=C–*H*), 8.38 (d, 2H, J=8.6 Hz, arom. Hs), 7.99 (d, 2H, J=8.5 Hz, arom. Hs); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 190.5 (C=O), 187.3 (C=O), 154.2 (C), 142.8 (q), 130.6 (2CH), 124.1 (2CH); Mass (ESI): 202.0 $(M+Na)^+$.

4.3. General procedure for the synthesis of ethyl β-aroylacrylates (10a–e) from *p*-substituted phenylglyoxals (8a–e)

The solution of ethoxycarbonyl-methyledinetriphenylphosphorane (2 g, **9**) in dry dichloromethane (DCM, 10 ml) was taken in the round bottom flask fitted with guard tube, and a solution of 1 equiv *p*-substituted phenylglyoxal (**8**) in DCM (5 mL) was added to it. The mixture was stirred for 4 h at room temperature. After the completion of reaction, which was monitored by TLC, the solvent was removed under reduced pressure and the contents stirred with hexane, and filtered. The filtrate was concentrated under vacuum and the obtained product mixtures were subsequently resolved by column chromatography: column packed in hexane (20 g, 60–120 mesh), eluted with hexane only to obtain the ethyl β-aroylacrylates (**10**) in good yields.

*4.3.1. Ethyl β-aroylacrylate (**10a**)*

Light yellow oil; yield 4.2 g, 91%; R_f ($CHCl_3$) 0.52; IR ($CHCl_3$): 1723, 1672, 1301, 1270, 1174 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 8.14 (dd, 2H, *J*=8.3 and 1.5 Hz, arom. Hs), 7.91 (d, 1H, *J*=15.5 Hz, olefinic CH), 7.66–7.47 (m, 3H, arom. Hs), 6.88 (d, 1H, *J*=15.5 Hz, olefinic CH), 4.30 (q, 2H, *J*=7.1 Hz, CH_2), 1.35 (t, 3H, *J*=7.1 Hz, CH_3); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 193.2 (C=O), 164.8 (C=O), 136.2 (q), 135.7 (CH), 133.3 (CH), 132.5 (CH), 128.9 (2CH), 128.4 (2CH), 60.8 (CH_2), 13.7 (CH_3); Mass (ESI): 227.4 $(M+Na)^+$. (Found: C, 70.65; H, 5.96. $C_{12}H_{12}O_3$ requires: C, 70.57; H, 5.92%.)

*4.3.2. p-Tolyl-ethyl-β-aroylacrylate (**10b**)*

Light yellow oil; yield 4.3 g, 90%; R_f ($CHCl_3$) 0.52; IR ($CHCl_3$): 1725, 1673, 1307, 1267, 1172 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 7.92 (d, 2H, *J*=7.8 Hz, arom. Hs), 7.86 (d, 1H, *J*=15.5 Hz, olefinic CH), 7.28 (d, 2H, *J*=7.2 Hz, arom. Hs), 6.86 (d, 1H, *J*=15.5 Hz, olefinic CH), 4.29 (q, 2H, *J*=7.0 Hz, CH_2), 2.41 (s, 3H, CH_3), 1.34 (t, 3H, *J*=7.1 Hz, CH_3); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 193.4 (C=O), 164.6 (C=O), 143.6 (C), 135.8 (CH), 134.1 (q), 132.6 (CH), 129.0 (2CH), 128.5 (2CH), 61.1 (CH_2), 20.9 (CH_3), 13.8 (CH_3); Mass (ESI): 241.1 $(M+Na)^+$. (Found: C, 71.59; H, 6.41. $C_{13}H_{14}O_3$ requires: C, 71.54; H, 6.47%.)

*4.3.3. p-Methoxy-ethyl-β-aroylacrylate (**10c**)*

Light yellow oil; yield 4.6 g, 93%; R_f ($CHCl_3$) 0.50; IR ($CHCl_3$): 1723, 1670, 1303, 1271, 1174 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 8.12 (d, 2H, *J*=8.8 Hz, arom. Hs), 7.96 (d, 1H, *J*=15.3 Hz, olefinic CH), 6.94 (d, 2H, *J*=8.8 Hz, arom. Hs), 6.83 (d, 1H, *J*=15.4 Hz, olefinic CH), 4.27 (q, 2H, *J*=7.1 Hz, CH_2), 3.87 (s, 3H, OCH_3), 1.35 (t, 3H, *J*=7.1 Hz, CH_3); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 193.3 (C=O), 168.4 (C), 164.2 (C=O), 135.8 (CH), 132.6 (CH), 131.2 (2CH), 129.0 (q), 114.3 (2CH), 60.7 (CH_2), 56.1 (CH_3), 13.8 (CH_3); Mass (ESI): 257.3 $(M+Na)^+$. (Found: C, 66.70; H, 6.07. $C_{13}H_{14}O_4$ requires: C, 66.66; H, 6.02%.)

*4.3.4. p-Bromo-ethyl-β-aroylacrylate (**10d**)*

Light yellow oil; yield 5.1 g, 91%; R_f ($CHCl_3$) 0.49; IR ($CHCl_3$): 1731, 1674, 1301, 1269, 1172 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 8.00 (d, 2H, *J*=8.8 Hz, arom. Hs), 7.93 (d, 1H, *J*=15.3 Hz, olefinic CH), 7.64 (d, 2H, *J*=8.4 Hz, arom. Hs), 6.87 (d, 1H, *J*=15.3 Hz, olefinic CH), 4.30 (q, 2H, *J*=7.1 Hz, CH_2), 1.35 (t, 3H, *J*=7.1 Hz, CH_3); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 193.3 (C=O), 164.8 (C=O), 136.1 (q), 135.6 (CH), 132.6 (CH), 132.3 (2CH), 131.7 (2CH), 128.9 (C), 59.8 (CH_2), 13.7 (CH_3); Mass (ESI): 306.8 $(M+Na)^+$. (Found: C, 50.95; H, 3.88. $C_{12}H_{11}BrO_3$ requires C, 50.91; H, 3.92%.)

*4.3.5. p-Nitro-ethyl-β-aroylacrylate (**10e**)*

Light yellow oil; yield 4.8 g, 92%; R_f ($CHCl_3$) 0.50; IR ($CHCl_3$): 1730, 1674, 1302, 1271, 1174 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 8.13 (d, 2H, *J*=8.6 Hz, arom. Hs), 7.95 (d, 1H, *J*=15.5 Hz, olefinic CH), 7.74 (d, 2H, *J*=8.5 Hz, arom. Hs), 6.85 (d, 1H, *J*=15.5 Hz, olefinic CH), 4.29 (q, 2H, *J*=7.1 Hz, CH_2), 1.35 (t, 3H, *J*=7.1 Hz, CH_3); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 193.5 (C=O), 165.0 (C=O), 155.8 (C), 141.6 (q), 135.6 (CH), 132.6 (CH), 131.2 (2CH), 124.6 (2CH), 60.3 (CH_2), 13.8 (CH_3); Mass (ESI): 272.2 $(M+Na)^+$. (Found: C, 57.90; H, 4.41; N, 5.57. $C_{12}H_{11}NO_5$ requires: C, 57.83; H, 4.45; N, 5.62%.)

4.4. General procedure for the synthesis of 1-aroyl-2,3-*cis*-diethoxycarbonylcyclopropanes (15a–e) from β-aroylacrylates (10a–e)

To ice cold solutions of dimethyl-ethoxycarbonlymethyl-oxosulfonium bromide (**13**, 2.00 g) in a mixture of dry THF (5 ml) and dry triethylamine (10 ml), stirred in three necked round bottomed flasks under nitrogen environment for 10 min, were added, drop wise through a dropping funnel, solution of β-acrylates (**10a–e**, 0.5 equiv), in dry THF (2 ml) over a period of 25 min; the contents were stirred for extended time and allowed to attain ambient temperature. Further contents were stirred till the completion of reaction (8 h). After the completion of reaction, monitored by TLC, the contents were partitioned between dichloromethane and water. The aqueous layer was further extracted with 2×20 ml of dichloromethane. The combined dichloromethane extracts were dried over anhydrous sodium sulfate, suspension was filtered and contents were distilled under reduced pressure. Subsequently, mixture was resolved by column chromatography, column packed in hexane (20 g, 60–120 mesh), eluted with hexane/ethylacetate (90:10).

*4.4.1. 1-Benzoylcyclopropane-2,3-dicarboxylic acid diethyl ester (**15a**)*

White crystalline solid (hexane/chloroform, 2:1), mp 43–45 °C; yield (2.4 g, 90%); R_f($CHCl_3$) 0.39; IR ($CHCl_3$): 1735, 1670, 1207 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 8.19 (dd, 2H, *J*=8.5 and 1.6 Hz, arom. Hs), 7.63–7.49 (m, 3H, arom. Hs), 4.21 (q, 4H, *J*=7.1 Hz, $2CH_2$), 3.75 (t, 1H, *J*=5.6 Hz, C1 H), 2.71 (d, 2H, *J*=5.6 Hz, C2,3 Hs), 1.31 (t, 6H, *J*=7.1 Hz, $2CH_3$); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 194.5 (C=O), 167.7 (2C=O), 136.4 (q), 133.6 (CH), 128.6 (2CH), 128.5 (2CH), 61.3 (CH_2), 30.0 (2C), 28.9 (C), 14.1 ($2CH_3$); Mass (ESI): 313.6 $(M+Na)^+$. (Found: C, 66.24; H, 6.28. $C_{16}H_{18}O_5$ requires: C, 66.19; H, 6.25%.)

*4.4.2. 1-(4-Methyl-benzoyl)-cyclopropane-2,3-dicarboxylic acid diethyl ester (**15b**)*

White oil; yield (2.3 g, 90%); R_f ($CHCl_3$) 0.36; IR ($CHCl_3$): 1728, 1672, 1217, 1180 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 7.99 (d, 2H, *J*=8.2 Hz, arom. Hs), 7.31 (d, 2H, *J*=7.8 Hz, arom. Hs), 4.20 (q, 4H, *J*=7.2 Hz, $2CH_2$), 3.75 (t, 1H, *J*=5.6 Hz, C1 H), 2.71 (d, 2H, *J*=5.6 Hz, C2,3 Hs), 2.44 (S, 3H, CH_3), 1.29 (t, 6H, *J*=7.1 Hz, $2CH_3$); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 194.2 (C=O), 167.9 (2C=O), 144.6 (C), 133.8 (q), 129.2 (2CH), 128.6 (2CH), 61.1 ($2CH_2$), 29.8 (2C), 28.7 (C), 21.4 (CH_3), 13.9 ($2CH_3$); Mass (ESI): 327.0 $(M+Na)^+$. (Found: C, 67.12; H, 6.67. $C_{17}H_{20}O_5$ requires: C, 67.09; H, 6.62%.)

*4.4.3. 1-(4-Methoxybenzoyl)cyclopropane-2,3-dicarboxylic acid diethyl ester (**15c**)*

White oil; yield 2.2 g, 91%; R_f ($CHCl_3$) 0.37; IR ($CHCl_3$): 1732, 1671, 1205, 1176 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 8.04 (d, 2H, *J*=8.8 Hz, arom. Hs), 6.94 (d, 2H, *J*=8.8 Hz, arom. Hs), 4.16 (q, 4H, *J*=7.1 Hz, $2CH_2$), 3.87 (s, 3H, OCH_3), 3.65 (t, 1H, *J*=5.6 Hz, C1 H), 2.64 (d, 2H, *J*=5.6 Hz, C2,3 Hs), 1.27 (t, 6H, *J*=7.1 Hz, $2CH_3$); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 193.2 (C=O), 168.2 (C), 164.1 (2C=O), 130.9 (2CH), 129.4 (q), 113.9 (2CH), 61.4 (CH_2), 55.5 (CH_3), 29.8 (2C), 28.8 (C), 14.1 ($2CH_3$); Mass (ESI): 343.3 $(M+Na)^+$. (Found: C, 63.78; H, 6.32. $C_{17}H_{20}O_6$ requires: C, 63.74; H, 6.29%.)

*4.4.4. 1-(4-Bromo-benzoyl)-cyclopropane-2,3-dicarboxylic acid diethyl ester (**15d**)*

White oil; yield 2.0 g, 90%; R_f ($CHCl_3$) 0.37; IR (KBr): 1731, 1681, 1205, 1178 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 8.07 (d, 2H, *J*=8.6 Hz,

arom. Hs), 7.03 (d, 2H, *J*=8.7 Hz, arom. Hs), 4.18 (q, 4H, *J*=7.2 Hz, $2CH_2$), 3.75 (t, 1H, *J*=5.6 Hz, C1 H), 2.71 (d, 2H, *J*=5.6 Hz, C2,3 Hs), 1.30 (t, 6H, *J*=7.1 Hz, $2CH_3$); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 194.0 (C═O), 167.8 (2C═O), 135.0 (q), 132.0 (2CH), 129.9 (2CH), 129.1 (C), 61.6 ($2CH_2$), 30.1 (2C), 28.9 (C), 14.0 ($2CH_3$); Mass (ESI): 391.4 $(M+Na)^+$. (Found: C, 52.07; H, 4.60. $C_{16}H_{17}BrO_5$ requires: C, 52.05; H, 4.64%.)

4.4.5. 1-(4-Nitro-benzoyl)-cyclopropane-2,3-dicarboxylic acid diethyl ester (**15e**)

White oil; yield 2.2 g, 89%; R_f ($CHCl_3$) 0.35; IR (KBr): 1732, 1668, 1234, 1188 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 8.05 (d, 2H, *J*=8.2 Hz, arom. Hs), 7.22 (d, 2H, *J*=8.5 Hz, arom. Hs), 4.20 (q, 4H, *J*=7.1 Hz, $2CH_2$), 3.75 (t, 1H, *J*=5.6 Hz, C1 H), 2.71 (d, 2H, *J*=5.6 Hz, C2,3 Hs), 1.29 (t, 6H, *J*=7.1 Hz, $2CH_3$); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 194.3 (C═O), 165.7 (2C═O), 152.8 (C), 136.5 (q), 133.5 (2CH), 129.7 (2CH), 61.0 (2CH2), 29.9 (2C), 28.7 (C), 14.1 ($2CH_3$); Mass (ESI): 358.3 $(M+Na)^+$. (Found: C, 57.35; H, 5.08; N, 4.21. $C_{16}H_{17}NO_7$ requires: C, 57.31; H, 5.11; N, 4.18%.)

4.5. General procedure for the synthesis of amide adducts (17a–e) from 1-aroyl-2,3-*cis*-diethoxycarbonylcyclopropanes (15a–e) under monomode-microwave irradiation

In a 250 ml round bottom flask, the trisubstituted cyclopropane adducts (300 mg, **15a–e**) and ethanolamine (**16**, 2.5 mol equiv) were dissolved in dichloromethane. To this solution different catalyst (1.00 g, silica gel G/neutral alumina/montmorillonite KSF) was added and the solvent was removed under vacuum to absorb the contents on the catalyst. The obtained powder was exposed to the microwave irradiation using the focused monomode-microwave (CEM-Discover) reactor. The round bottom flask containing powder of contents fitted with condenser was placed in the cavity of the microwave reactor. The mouth of the cavity was covered with the cavity lid. Then it was exposed to the microwave irradiation. In the case of catalyst silica gel, microwave irradiation was done for 3–8 min (1–3 min for running time and 2–5 min for holding time) by using 150–180 W power at 123–165 °C. For the catalyst neutral alumina, the microwave irradiation was done for 5 min (2 min for running time and 3 min for holding time) by using 150 W power at 123 °C. In the case of montmorillonite KSF, the microwave irradiation was done for 3 min (1 min for running time and 2 min for holding time) by using 150 W power at 121 °C. In each case, the adsorbed material was then extracted with 3×30 ml methanol and dried over anhydrous sodium sulfate (Na_2SO_4). The solvent was then distilled off under reduced pressure. The products were isolated by flash column chromatographic separation, column packed in chloroform (230–400 mesh, 10 g), eluted with Chloroform/methanol (60:40). The products were obtained in 30–35% and 73–75% yield, in the case of the catalyst silica gel G and neutral alumina, respectively, and in excellent yields (91–94%) for the catalyst montmorillonite KSF.

4.5.1. 1-Benzoyl-cyclopropane-2,3-dicarboxylic acid bis-[(2-hydroxy-ethyl)-amide] (**17a**)

White solid (hexane/chloroform/methanol, 4:2:1), mp 81–83 °C; R_f (CH_3OH) 0.16; IR (KBr): 3334, 3309, 1674, 1647, 1558, 1215 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz): δ 8.11 (dd, 2H, *J*=8.25 and 1.5 Hz, arom. Hs), 7.78 (br s, 2H, N*H*s), 7.64–7.38 (m, 3H, arom, Hs), 3.86 (t, 1H, *J*=5.4 Hz, C1 H), 3.72–3.58 (m, 4H, 2C*H*$_2$–OH), 3.49–3.41 (m, 2H, C*H*$_2$–NH), 3.34–3.26 (m, 2H, C*H*$_2$–NH), 2.68 (d, 2H, *J*=5.4, C2,3 Hs), 2.59 (br s, 2H, O*H*s); ^{13}C NMR (DMSO, 75 MHz): δ 195.8 (C═O), 167.9 (2C═O), 136.0 (q), 133.0 (CH), 128.1 (2CH), 128.0 (CH), 60.2 ($2CH_2$), 42.0 ($2CH_2$), 32.0 (2C), 29.0 (C); Mass (ESI): 343.0 $(M+Na)^+$. (Found: C, 59.93; H, 6.32; N, 8.79. $C_{16}H_{20}N_2O_5$ requires: C, 59.99; H, 6.29; N, 8.74%.)

4.5.2. 1-(4-Methyl-benzoyl)-cyclopropane-2,3-dicarboxylic acid bis-[(2-hydroxy-ethyl)-amide] (**17b**)

White solid (hexane/chloroform/methanol, 4:2:1), mp 89–93 °C; R_f (CH_3OH) 0.16; IR (KBr): 3419, 3353, 1672, 1660, 1556, 1307, 1184 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz): δ 8.11 (d, 2H, *J*=7.5 Hz, arom. Hs), 7.96 (br s, 2H, N*H*s), 7.61 (d, 2H, *J*=7.2 Hz, arom. Hs), 3.85 (t, 1H, *J*=5.4 Hz, C1 H), 3.65–3.56 (m, 4H, 2C*H*$_2$–OH), 3.41–3.38 (m, 2H, C*H*$_2$–NH), 3.36–3.30 (m, 2H, C*H*$_2$–NH), 2.66 (d, 2H, *J*=5.4 Hz, C2,3 Hs), 2.60 (br s, 2H, O*H*s), 1.97 (s, 3H, CH_3); ^{13}C NMR (DMSO, 75 MHz): δ 195.9 (C═O), 167.8 (2C═O), 136.1 (C), 133.0 (q), 128.1 (2CH), 128.0 (2CH), 60.1 ($2CH_2$), 42.0 ($2CH_2$), 31.9 (2C), 29.0 (C), 28.0 (CH_3); Mass (ESI): 357.0 $(M+Na)^+$. (Found: C, 61.11; H, 6.60; N, 8.36. $C_{17}H_{22}N_2O_5$ requires: C, 61.07; H, 6.63; N, 8.38%.)

4.5.3. 1-(4-Methoxybenzoyl)-cyclopropane-2,3-dicarboxylic acid bis-[(2-hydroxy-ethyl)-amide] (**17c**)

White solid (hexane/chloroform/methanol, 4:2:1), mp 154–157 °C; R_f (CH_3OH) 0.16; IR (KBr): 3431, 3359, 1664, 1650, 1556, 1255, 1186 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz): δ 8.00 (d, 2H, *J*=8.1 Hz, arom. Hs), 7.92 (br s, 2H, N*H*s), 7.29 (d, 2H, *J*=7.8 Hz, arom. Hs), 3.88 (s, 3H, OCH_3) 3.81 (t, 1H, *J*=5.4 Hz, C1 H), 3.74–3.57 (m, 4H, 2C*H*$_2$–OH), 3.46–3.38 (m, 2H, C*H*$_2$–NH), 3.29–3.18 (m, 2H, C*H*$_2$–NH), 2.79 (br s, 2H, O*H*s), 2.64 (d, 2H, *J*=5.5 Hz, C2,3 Hs); ^{13}C NMR (DMSO, 75 MHz): δ 195.3 (C═O), 167.8 (2C═O), 143.8 (C), 133.6 (q), 128.7 (2CH), 128.1 (2CH), 60.1 ($2CH_2$), 42.0 ($2CH_2$), 31.8 (2C), 27.8 (C), 21.0 (CH_3); Mass (ESI): 373.1 $(M+Na)^+$. (Found: C, 58.33; H, 6.36; N, 8.19. $C_{17}H_{22}N_2O_6$ requires: C, 58.28; H, 6.33; N, 8.23%.)

4.5.4. 1-(4-Bromo-benzoyl)-cyclopropane-2,3-dicarboxylic acid bis-[(2-hydroxy-ethyl)-amide] (**17d**)

White solid (hexane/chloroform/methanol, 4:2:1), mp 154–157 °C; R_f (CH_3OH) 0.16; IR (KBr): 3423, 3314, 1670, 1649, 1557, 1232, 1181 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz): δ 8.00 (d, 2H, *J*=8.7 Hz, arom. Hs), 7.86 (br s, 2H, N*H*s), 7.64 (d, 2H, *J*=8.4 Hz, arom. Hs), 3.79 (t, 1H, *J*=5.4 Hz, C1 H), 3.70–3.56 (m, 4H, 2C*H*$_2$–OH), 3.48–3.31 (m, 2H, C*H*$_2$–NH), 3.30–3.22 (m, 2H, C*H*$_2$–NH), 2.67 (d, 2H, *J*=5.4 Hz, C2,3 Hs), 2.59 (br s, 2H, O*H*s); ^{13}C NMR (DMSO, 75 MHz): δ 195.4 (C═O), 167.7 (2C═O), 135.0 (q), 131.4 (2CH), 129.7 (2CH), 129.1 (C), 60.2 ($2CH_2$), 42.1 (2CH2), 32.1 (2C), 28.0 (C); Mass (ESI): 421.0 $(M+Na)^+$. (Found: C, 48.10; H, 4.85; N, 7.06. $C_{16}H_{19}BrN_2O_5$ requires: C 48.13, H 4.80, N 7.02%.)

4.5.5. 1-(4-Nitro-benzoyl)-cyclopropane-2,3-dicarboxylic acid bis-[(2-hydroxy-ethyl)-amide] (**17e**)

White solid (hexane/chloroform/methanol, 4:2:1), mp 152–154 °C; R_f (CH_3OH) 0.16; IR (KBr): 3437, 3349, 1668, 1650, 1558, 1255, 1184 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz): δ 8.01 (2H, d, *J*=8.6 Hz, arom. Hs), 7.94 (2H, br s, N*H*s), 7.63 (2H, d, *J*=8.3 Hz, arom. Hs), 3.81 (1H, t, *J*=5.4 Hz, C1 H), 3.73–3.57 (4H, m, 2C*H*$_2$–OH), 3.48–3.33 (2H, m, C*H*$_2$–NH), 3.29–3.21 (2H, m, C*H*$_2$–NH), 2.65 (2H, d, *J*=5.7 Hz, C2,3 Hs), 2.60 (br s, 2H, O*H*s); ^{13}C NMR (DMSO, 75 MHz): δ 195.3 (C═O), 167.8 (2C═O), 151.9 (C), 136.3 (q), 129.5 (2CH), 127.6 (2CH), 60.3 ($2CH_2$), 42.1 ($2CH_2$), 32.0 (2C), 28.1 (C); Mass (ESI): 358.1 $(M+Na)^+$. (Found: C, 52.54; H, 5.30; N, 11.46. $C_{16}H_{19}N_3O_7$ requires: C, 52.60; H, 5.24; N, 11.50%.)

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2008.10.058.

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