

Organic Synthesis and Current Understanding of the Mechanisms of the CFTR Modulator Drugs Ivacaftor, Tezacaftor, and Elexacaftor

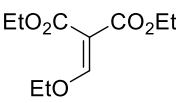
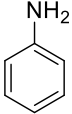
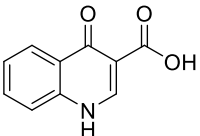
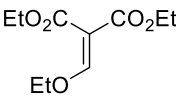
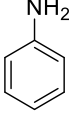
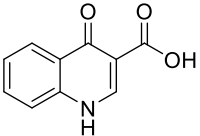
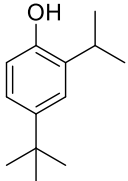
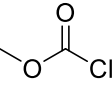
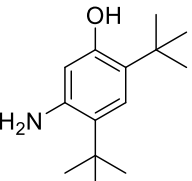
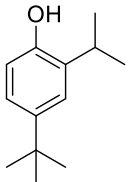
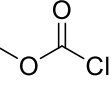
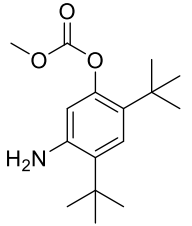
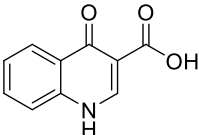
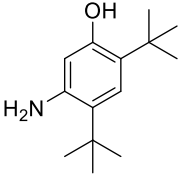
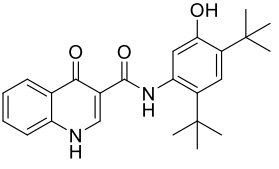
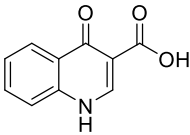
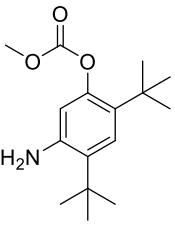
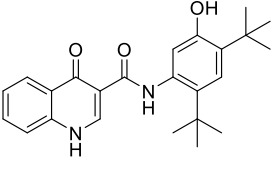
Filipa C. Ferreira ¹, Camilla D. Buarque ^{2,*} and Miquéias Lopes-Pacheco ^{1,*}

¹ Biosystems & Integrative Sciences Institute (BioISI), Faculty of Sciences University of Lisbon, 1749-016 Lisbon, Portugal

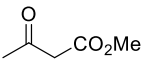
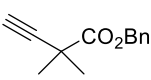
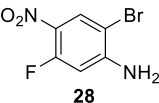
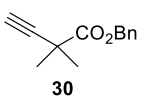
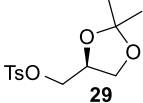
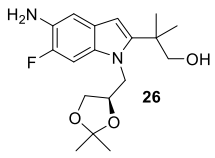
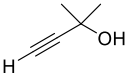
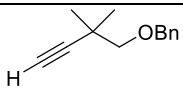
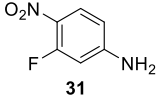
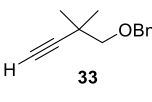

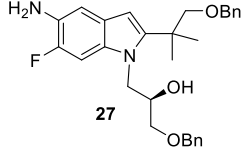
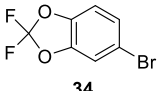
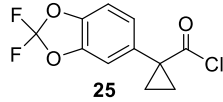
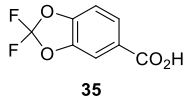
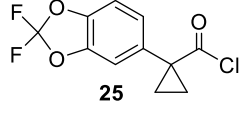
² Department of Chemistry, Pontifical Catholic University of Rio de Janeiro (PUC-Rio), 22435-900 Rio de Janeiro, RJ, Brazil

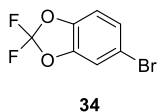
* mlpacheco@fc.ul.pt (M.L.-P.), camilla-buarque@puc-rio.br (C.D.B.)

Supplementary Table S1. Summary of the synthetic methods and conditions of the reactions of ivacaftor

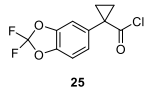
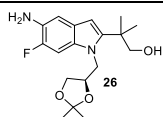
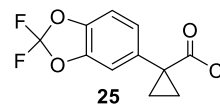
Approach	Substrate A	Substrate B	Reaction conditions	Product
1	 8	 9	1) 140-150 °C, 2h 2) POCl ₃ , PPA, 70 °C, 4h (70%) 3) NaOH, reflux, 92%	 4a
2	 8	 9	1) 110 °C, 2.5h, neat 2) phenyl ether 228-232 °C, 1.5h 3) 2N NaOH, ethanol, reflux, 16h	 4a
1	 21	—	1)  Et ₃ N, DMAP, CH ₂ Cl ₂ , 0-25 °C (100%) 2) HNO ₃ /H ₂ SO ₄ 3) KOH/MeOH (2 steps) (29%) 4) HCO ₂ NH ₄ EtOH, Pd/C (100%)	 5a
2	 21	—	1)  Et ₃ N, DMAP, CH ₂ Cl ₂ , 0-25 °C (100%) 2) HNO ₃ /H ₂ SO ₄ , CH ₂ Cl ₂ , -5-0 °C 3) Pd/C, H ₂ , MeOH 25 °C	 5b
1	 4a	 5a	HATU, Et ₃ N, DMF (71%)	 IVACAFTOR (1)
2	 4a	 5b	1) T3P, pyr, 2-MeTHF 2) NaOH, MeOH	 IVACAFTOR (1)

Supplementary Table S2. Summary of the synthetic methods and conditions of the reactions of tezacaftor

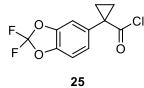
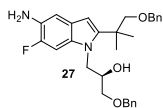
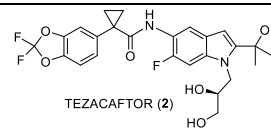
Approach	Substrate A	Substrate B	Reaction conditions	Product
1		—	1) NaH, MeI, THF (53%) 2) PCl ₅ , DMF (cat), CH ₂ Cl ₂ , reflux (82%) 3) aq. NaOH, reflux (44%) 4) NaNH ₂ , DMSO (94%) 5) BnOH, DCC, CH ₂ Cl ₂ (59%)	
1			1) Pd(PPh ₃) ₂ Cl ₂ , Et ₃ N, CuI, 80 °C (56%) 2) PdCl ₂ , CH ₃ CN, 80 °C (90%) 3)  , Cs ₂ CO ₃ , DMF, 80 °C 4) LiAlH ₄ , THF (87%, 2 steps) 5) H ₂ , Pd/C, EtOH (78%)	
2		—	1) HCl conc. (90%) 2) a) Mg, THF; b) BnOCH ₂ Cl 3) KOH, MeOH	
2			1) NBS, EtOAc (50%) 2)  , Zn(ClO ₄) ₂ ·2H ₂ O, toluene, 4 Å MS, 80 °C 3) a) H ₂ , Pt(S)/C, <i>i</i> -PrOAc, 30 °C; b) p-TsOH-H ₂ O, CH ₂ Cl ₂ 4) 33, Pd(OAc) ₂ , dppb, K ₂ CO ₃ , CH ₃ CN, 80 °C	
1		—	1) CO, Et ₃ N, Pd(PPh ₃) ₄ , CH ₃ CN, MeOH, 75 °C 2) LiAlH ₄ , THF (76%, 2 steps) 3) a) SOCl ₂ , CH ₂ Cl ₂ ; b) NaCN, DMSO 4) ClCH ₂ CH ₂ Br, BnNEt ₃ Cl, NaOH, 70 °C 5) 10% aq. NaOH, reflux (1.6%, 4 steps)	
1		—	1) a) NaAlH ₂ (OCH ₂ CH ₂ OCH ₃), toluene; b) 10% aq. NaOH (86-92%) 2) SOCl ₂ , DMAP, MTBE (82-100%) 3) NaCN, DMSO, 30-40 °C (95-100%) 4) ClCH ₂ CH ₂ Br, Oct ₄ NBr, 50% KOH, 70 °C (88-100%) 5) 6N NaOH, EtOH, 80 °C (69%) 6) SOCl ₂ , DMF	



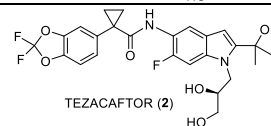
- 1) NC(=O)OCC, Pd(dba)₂, *t*-Bu₃P, 70 °C, Na₃PO₄, toluene/H₂O
- 2) HCl 3N, DMSO, 75 °C (66%, 2 steps)
- 3) ClCCBr, Oct₄NBr, 50% KOH, 70 °C (88-100%)
- 4) 6N NaOH, EtOH, 80 °C (69%)
- 5) SOCl₂, DMF



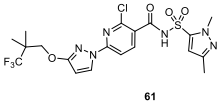
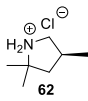
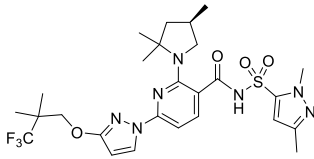
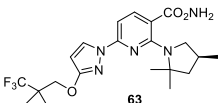
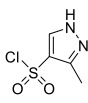
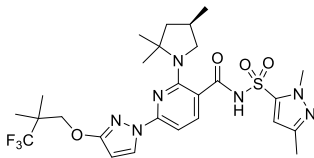
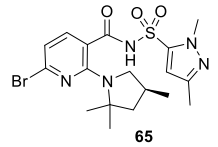
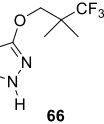
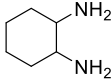
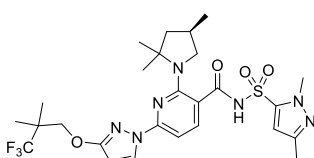
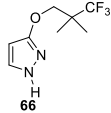
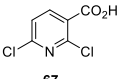
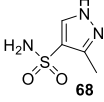
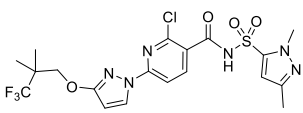
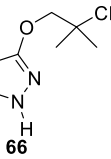
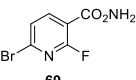
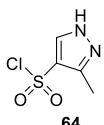
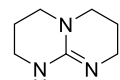
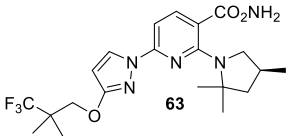
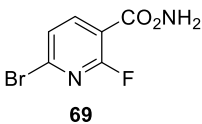
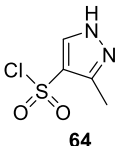
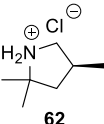
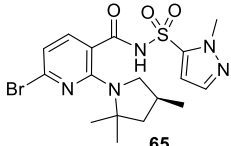
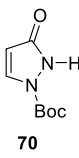
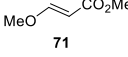
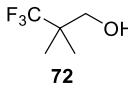
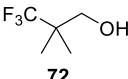
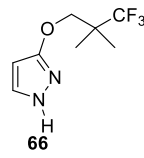
- 1) Et₃N, CH₂Cl₂ (100%)
- 2) *p*-TsOH-H₂O, MeOH, H₂O, 80 °C (47%)

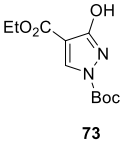
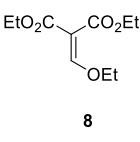
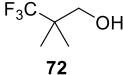
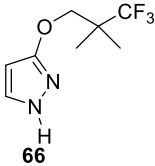
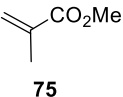


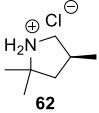
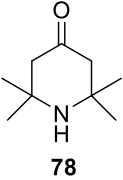
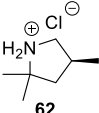



- 1) Et₃N, toluene/CH₂Cl₂ (100%)
- 2) H₂, Pd/C, MeOH (63-84%)



Supplementary Table S3. Summary of the synthetic methods and conditions of the reactions of elxacaftor

Approach	Substrate A	Substrate B	Substrate C	Reaction conditions	Product
1			—	K ₂ CO ₃ , DMSO, DEE, 120 °C 90%	 ELEXACAFITOR (3)
1			—	Li, <i>t</i> -amonoxide, 2-MeTHF	 ELEXACAFITOR (3)
2			—	 /CuI	 ELEXACAFITOR (3)
1				1) K ₂ CO ₃ , DABCO, DMF, rt (99%) 2) CDI, DBU, THF (93%)	 61
2				MEK, 80°C,  / <i>t</i> -BuXPhosPd G3	 63
2				Li, <i>t</i> -amonoxide, 2-MeTHF	 65
1				1) a) NH ₂ NH ₂ , H ₂ O, MeOH, 40 °C; b) 2) (Boc) ₂ O, Et ₃ N, rt (71%) 2)  3) DIAD, PPh ₃ , toluene, 110 °C (57%)	 66

2				<p>1) a) NH_2NH_2, H_2O, EtOH; b) 2) $(\text{Boc})_2\text{O}$, Et_3N, rt (59%)</p> <p>2) DIAD, PPh_3, toluene, 105°C</p> <p>3) a) KO-t-Bu</p> <p>b) H_2O, 2-MeTHF, $40-50^\circ\text{C}$, (79%, 2 steps)</p>	
1			—	<p>1)  DBU, THF, 50°C (99%)</p> <p>2) Palatase Lipase, pH 6.5, 32°C (45%)</p> <p>3) H_2, RaNi, EtOH, 60°C (87%)</p> <p>4) a) LiAlH_4, THF, $60-63^\circ\text{C}$; b) 2) HCl aq. 2-PrOH (75%)</p>	
2		—	—	<p>1) $\text{Me}_3\text{Bu}_3\text{NCl}$, NaOH, CHCl_3, CH_2Cl_2</p> <p>2) HCl, CH_2Cl_2 (55%)</p> <p>3) $[\text{Rh}(\text{nbd})\text{Cl}]\text{Cl}$ 2MandyPhos, 5 bar H_2, THF, 25°C or $[\text{RuCl}(\text{p-cymeme}\{(\text{R})\text{-segphps}\})\text{Cl}$, THF, 45 bar H_2, 30°C (91-92%)</p> <p>4) a) LiAlH_4, THF, $60-63^\circ\text{C}$; b) 2) HCl aq. 2-PrOH (75%)</p>	
2		—	—	<p>1) LDA, DMPU, TBS-Cl, THF, -70°C (83%)</p> <p>2) $\text{Ru}(\text{bpy})_3\text{Cl}_2 \cdot 6\text{H}_2\text{O}$, pyrrolidine, CH_3CN, EtOH, CF_3I, LED, 440-445 nm</p> <p>3) a) NaOH, 50°C; b) HCl/hexane, 3) Morpholine (73%)</p> <p>4) LiAlH_4, THF (79%)</p>	